

**Basics in
PHARMACOLOGY
for Dental Students**

VISIT...

LANZAROTE
Caliente.COM

Basics in PHARMACOLOGY for Dental Students

Arvind Singh Panwar MD

Associate Professor
Department of Pharmacology
Government Medical College, Surat
Ex-consulting Clinical Pharmacologist
Sahajanand Biotech Pvt Ltd, Surat, INDIA/USA

Editorial Board

ND Kantharia MD
Preeti P Yadav MD
Chetna Patel MD
Sejal Patel MD
Anita Sinha MD
Kirtida Tandel MD



JAYPEE BROTHERS MEDICAL PUBLISHERS (P) LTD

Ahmedabad • St Louis (USA) • Panama City (Panama) • London (UK) • New Delhi
Bengaluru • Chennai • Hyderabad • Kochi • Kolkata • Lucknow • Mumbai • Nagpur

Published by

Jitendar P Vij

Jaypee Brothers Medical Publishers (P) Ltd

Corporate Office

4838/24 Ansari Road, Daryaganj, **New Delhi** - 110002, India, Phone: +91-11-43574357,
Fax: +91-11-43574314

Registered Office

B-3 EMCA House, 23/23B Ansari Road, Daryaganj, **New Delhi** - 110 002, India
Phones: +91-11-23272143, +91-11-23272703, +91-11-23282021
+91-11-23245672, Rel: +91-11-32558559, Fax: +91-11-23276490, +91-11-23245683
e-mail: jaypee@jaypeebrothers.com, Website: www.jaypeebrothers.com

Offices in India

- **Ahmedabad**, Phone: Rel: +91-79-32988717, e-mail: ahmedabad@jaypeebrothers.com
- **Bengaluru**, Phone: Rel: +91-80-32714073, e-mail: bangalore@jaypeebrothers.com
- **Chennai**, Phone: Rel: +91-44-32972089, e-mail: chennai@jaypeebrothers.com
- **Hyderabad**, Phone: Rel: +91-40-32940929, e-mail: hyderabad@jaypeebrothers.com
- **Kochi**, Phone: +91-484-2395740, e-mail: kochi@jaypeebrothers.com
- **Kolkata**, Phone: +91-33-22276415, e-mail: kolkata@jaypeebrothers.com
- **Lucknow**, Phone: +91-522-3040554, e-mail: lucknow@jaypeebrothers.com
- **Mumbai**, Phone: Rel: +91-22-32926896, e-mail: mumbai@jaypeebrothers.com
- **Nagpur**, Phone: Rel: +91-712-3245220, e-mail: nagpur@jaypeebrothers.com

Overseas Offices

- **North America Office, USA**, Ph: 001-636-6279734, e-mail: jaypee@jaypeebrothers.com, anjulav@jaypeebrothers.com
- **Central America Office, Panama City, Panama**, Ph: 001-507-317-0160, e-mail: cservice@jphmedical.com
Website: www.jphmedical.com
- **Europe Office, UK**, Ph: +44 (0) 2031708910, e-mail: info@jpmedpub.com

Basics in Pharmacology for Dental Students

© 2010, Jaypee Brothers Medical Publishers (P) Ltd.

All rights reserved. No part of this publication and DVD-ROM should be reproduced, stored in a retrieval system, or transmitted in any form or by any means: electronic, mechanical, photocopying, recording, or otherwise, without the prior written permission of the author and the publisher.

This book has been published in good faith that the material provided by author is original. Every effort is made to ensure accuracy of material, but the publisher, printer and author will not be held responsible for any inadvertent error(s). In case of any dispute, all legal matters are to be settled under Delhi jurisdiction only.

First Edition: 2010

ISBN 978-93-80704-30-2

Typeset at JPBMP typesetting unit

Printed at

Dedicated to

*Almighty God
and
My Respected Parents*

Foreword

Pharmacology, the “Science of Drugs”, forms a part of regular curriculum of many streams like medical, dental, pharmacy and veterinary courses at undergraduate as well as postgraduate levels. Though the fundamentals of drug action form an essential part of pharmacology teaching in every discipline, other components are required to be focused according to the need and scope of that particular branch. Hence, the contents and their presentation have to be specifically designed for the respective users. A balance between the essential details and not so important details has to be maintained. Over and above, the language must be easy to comprehend and treatise should be interesting enough. Side by side, highlighting of important aspect is also necessary.

This book “*Basics in Pharmacology for Dental Students*” is intended to be a textbook of pharmacology for the undergraduate students of dentistry and to my understanding, it meets with all the above-mentioned yardsticks. I hope it will be a useful companion for the teachers and will be able to fulfill the need of the students in making them proficient according to the prescribed syllabus and guide them in their future clinical practice.



SK Vajpeyee MD

Senior Professor of Pharmacology
Dean, Government Medical College &
New Civil Hospital
Surat, India

Preface

Dear Students,

While studying pharmacology in my third MBBS, I often experienced the overwhelming need for a good, updated, single, complete exam-oriented book of pharmacology, incorporating and intensifying many basics to face the exams in a more planned manner. This book is a sincere effort by me to fill the void, especially in pharmacology for dental students (BDS & MDS) and professionals.

It has been my constant endeavor to ensure that this book is very much exam oriented for both undergraduate and postgraduate dental students while containing a wealth of details to facilitate better understanding of the subject.

A primary strength to this book is that it incorporates all the details in very simple and explanatory sentences (points). Emphasis has been placed on good presentation of the topics by maintaining the continuity of the text. Explanatory sketches, diagrams and photographs are there, wherever needed. Keywords are highlighted in the bold prints.

While no stones have been left unturned to make this book error free, I sincerely apologize for any mistake that may have escaped my notice.

I truly hope my sincere efforts will be appreciated by you.

Arvind Singh Panwar

Acknowledgments

First and foremost, I wish to express my grateful thanks to the almighty god and my parents for the aspiration and inspiration, then I extend my sincere thanks and gratitude to my respected teachers for their blessings, encouragement and useful suggestions.

- Dr SK Vajpeyee, MD, Dean, Govt Medical College, Surat
- Dr BK Shah, MD (Pharmacol), Ex Prof & Head, Pharmac, MPSMC, Jamnagar
- Dr SD Mistry MD (Pharmacol) Prof & Head, Dept of Pharmac, MPSMC, Jamnagar
- Dr JG Buch, MD (Pharmacol), Prof & Head, Dept of Pharmac, Rajkot
- Dr VH Bhavsar, MD (Pharmacol), Prof, Dept of Pharmac, SAIMS, Indore
- Dr ND Kantharia, MD, Prof and Head (Pharmacol), Govt Med College, Surat
- Dr Ratan K Srivastava, MD, Professor & Head (Community Medicine), IMS, BHU, Varanasi
- Dr Bhagwat Sir, Ex Prof & Head, MGM Medical College, Indore
- Dr Tripathi, MD, Professor & Head, GMC, Bhavnagar

My expression and emotion fails to find words when I think of my family members for their unconditional support and has been a source of inspiration for me to hard work.

- Parents Late Thakur Bhagwansingh Panwar
 Mrs Swaroop Panwar
- Brothers Mr Dilip Singh Panwar, Mr Kishore Singh Panwar
- Wife Shivani
- Daughter Shreya
- Son Vedang

I will always remain grateful to you all for your moral support and encouragement

1. Dr Rahul Rokde, DA, Dept of PSM, MGMMC, Indore
2. Dr Pankaj Vyas, MS (Ortho), Indore
3. Dr Vijay Soni, MS, (Bombay Hospital), Indore
4. Dr Vivek Jha, MS, Urologist (Bombay Hospital), Indore
5. Dr Prashant Mishra, MS (McH CVTS), KEM, Mumbai
6. Dr Agrawal, Prem Neyati & Dr Fadnis, MD, Pharmacol, MGMMC, Indore
7. Dr Trevedi, Dr Dinesh Parmar, Dr Bhargava, Dr Gajera, Mrs Smita, Mrs Bhartiben, Dr Vaghela, MP Shah Medical College, Jamnagar
8. Dr NK Managoli, Dr Arvind Badiger, Sahajanand Biotech Pvt Ltd, Surat
9. Dr Vinod Shah, National Vice President, IMA, Surat
10. Dr Rajesh (Vidyasagar Coaching Classes), Dr Bhatia (Bhatia Coaching Classes)
11. Dr Chhaya Goyal, MD, Prof & Head, Dept of Pharmac, SAIMS, Indore
12. Dr Prashant, Dr Neyati, Dr Amol, Dr Chandresh, GMC, Baroda
13. Dr SK Srivastava, Professor & Head, SMC, Surat
14. Dr Anupama Desai, MD, Pharmacol, SMC, Surat
15. Dr Dimple Mapara, Prof & Head, Pharmacology, Surendranagar
16. Dr Ranjit Akolaker, MS, O & G, USA
17. Dr Bhagwansingh Thakur and Dr Ashish Jain, Choithram Hospital, Indore

18. Dr Mathur, Dr Khilnani, Dr Sharma, MD, Pharmacology, Rajasthan
19. Mr Kailash Pandey, Regional Manager, PDPL, Indore.
20. Late Dr Rajesh Verma, MD, Assist Prof, Physiology, Indore.

I would like to express gratitude to my friends, Dr Pankaj Vyas, Dr Suraj, Dr Amit, Dr Rahul, Dr Sunit, Dr Chetan, Dr P Yadav, Mr Joshiji, Dr A Jaiswal, Dr Jaikaran, Dr Sanjay, Dr Rupam, Dr Anil Singh, Dr Dhara Shah, Dr Chirag, Dr Amita, Dr Nikesh Patel, Dr Sanjay Aggarwal, Dr Jairaj Hanspal, Dr B Diwakar, Dr Daxa, Dr Nilesh, Dr Lokesh, Dr Mayur, Dr Shashank, Dr J Gupta, Dr Deepak Saxena, Dr Sanjeev Rao, Karamjeet Singh Gill and all our colleagues and friends, who had been constant source of encouragement.

Finally, thanks are due to our Publishers Shri Jitendar P Vij, Mr Tarun Duneja and Mr Bhupesh Arora, Mr KK Raman, Mr Sunil Dogra, Mr Pawan Kishore Tiwari and their team for preparing such a nice presentation.

Last but not the least, we wish to record our thanks to all those, who have helped us in this endeavor but their names are unintentionally omitted.

Arvind Singh Panwar

Contents

Abbreviations

SECTION 1: GENERAL PHARMACOLOGY

1.	Introduction	3
2.	Sources of drugs, nomenclature and essential drugs	5
3.	New drug discovery and development	7
4.	Routes of drug administration	11
5.	Pharmacokinetics	17
6.	Pharmacodynamics	36
7.	Factors modifying dosage and drug action	47
8.	Adverse drug reaction (ADR) and poisoning	50
9.	Drug interactions	54
10.	Rational prescription writing in dentistry	57
11.	Gene therapy	61

SECTION 2A: AUTONOMIC NERVOUS SYSTEM

1.	Introduction to autonomic pharmacology	67
2.	Adrenergic system	71
3.	Adrenergic drugs (sympathomimetics)	75
4.	Adrenergic antagonists (sympatholytics)	83
5.	Cholinergic system and drugs	89
6.	Anticholinergic drugs	97

SECTION 2B: PERIPHERAL NERVOUS SYSTEM

1.	Skeletal muscle relaxants	103
2.	Local anesthetics	107

SECTION 3: AUTACOIDS

1.	Autacoids: Histamine and antihistaminics	117
2.	Eicosanoids and platelet activating factor	120
3.	5-HT (Hydroxytryptamine) ergot alkaloids, angiotensins and kinins	123

SECTION 4: RESPIRATORY SYSTEM

1.	Cough and its management	129
2.	Bronchial asthma and its management	132

SECTION 5: BLOOD

1.	Drugs affecting hematopoiesis	139
2.	Hyperlipidemia and hypolipidemics (Antihyperlipidemic agents)	145
3.	Drugs used in the disorders of coagulation	150

SECTION 6: EXCRETORY SYSTEM

1.	Diuretic agents	161
2.	Antidiuretic drugs	167

SECTION 7: CARDIOVASCULAR SYSTEM

1.	Hypertension and antihypertensive drugs	171
2.	Cardiac glycosides and the drugs used in the treatment of congestive cardiac failure	181
3.	Drugs used in the treatment of angina pectoris and ischemia	188
4.	Cardiac arrhythmia and antiarrhythmic drugs	195
5.	Shock and its management	200
6.	Plasma expanders	203

SECTION 8: ENDOCRINOLOGY

1.	Hypothalamic and pituitary hormones	207
2.	Thyroid hormones and antithyroid drugs	214
3.	Agents affecting bone-mineral turnover	220
4.	Diabetes mellitus, insulin and oral hypoglycemic agents	224
5.	Corticotropin and the adrenal steroids	231

- 6. Estrogens, progestins and oral contraceptive 238
- 7. Androgens and anabolic steroids 244

SECTION 9: DRUGS ACTING ON UTERUS

- 1. Uterine stimulants 249
- 2. Uterine relaxants (Tocolytic agents) 251

SECTION 10: GASTROINTESTINAL SYSTEM

- 1. Dyspepsia, peptic ulcers and their management 255
- 2. Abdominal colic, emetics and antiemetics 260
- 3. Prokinetic agents 263
- 4. Drugs for constipation and diarrhea 265

SECTION 11: CENTRAL NERVOUS SYSTEM

- 1. Alcohol 271
- 2. Chemical transmission in the nervous system 276
- 3. Drugs used in Parkinson's disease and Alzheimer's disease 279
- 4. General anesthetics 284
- 5. Sedative hypnotics 293
- 6. Antiepileptics 299
- 7. Antianxiety drugs (anxiolytics), antidepressants and mood stabilizers 307
- 8. Drugs used in psychiatric disorders: Antipsychotics 316
- 9. Narcotic analgesics and antagonists 321
- 10. Central nervous system stimulants and psychotomimetics 331
- 11. Nonsteroidal anti-inflammatory drugs (NSAIDS) 334
- 12. Drugs used in rheumatoid arthritis and gout 348

SECTION 12: CHEMOTHERAPY

- 1. General consideration 357
- 2. Sulfonamide and cotrimoxazole 363

- 3. Beta-lactam antibiotics 367
- 4. Broad spectrum antibiotics 374
- 5. Aminoglycosides 379
- 6. Macrolides and other antibiotics 383
- 7. Quinolones and fluoroquinolones 386
- 8. Chemotherapy of urinary tract infections 389
- 9. Miscellaneous antibiotics 391
- 10. Chemotherapy of tuberculosis 393
- 11. Chemotherapy of leprosy 399
- 12. Antiviral drugs 402
- 13. Antifungal drugs 411
- 14. Antiamebic drugs 415
- 15. Chemotherapy of malaria 419
- 16. Anthelmintics 425
- 17. Drugs for trypanosomiasis and leishmaniasis 429
- 18. Immunostimulants and immunosuppressants 431
- 19. Drugs of choice 433

SECTION 13: CANCER CHEMOTHERAPY

- 1. Cancer chemotherapy 443

SECTION 14: DENTAL PHARMACOLOGY

- 1. Dental pharmacology and therapeutics 453

SECTION 15: MISCELLANEOUS DRUGS

- 1. Chelating agents 467
- 2. Antiseptics and disinfectants 469
- 3. Vaccines and antisera 475
- 4. Nutrients and vitamins 484
- Appendix 491
- Glossary 495
- References for further study 509
- Index 511



S E C T I O N

1

General Pharmacology

Introduction

The word **Pharmacology** is derived from the Greek words *Pharmakon*, which means “**an active principle**” (drugs), and *logos* which means a study/knowledge.

DEFINITION

Pharmacology is a branch of science, which deals with the detailed study of effective and safe use of the drugs, for medicinal purposes [Particularly their action on living animals organs or tissues].

The action may be beneficial or harmful.

Pharmacology is an integrated rather than an autonomous science. The techniques and knowledge of several disciplines such as physiology, biochemistry, physics, chemistry and even mathematics have been incorporated to make the subject easier and well defined.

Practically **Pharmacology** deals with the knowledge about drugs, which includes their sources, chemical structure, dosage, form, route of administration, pharmacokinetics, pharmacodynamics, frequency of administration, indications (uses), contraindications, adverse effects and the drug interactions.

WHAT IS DRUG?

It is any substance that affects a biological system in a potentially useful way.

Drug: The word ‘**drug**’ is derived from a French word ‘*Droque*’ – a dry herb. In general, **a drug is defined as any substance (natural or synthetic) used for the purpose of diagnosis, prevention and relief or cure of any disease in men or animals.**

In 1966, **WHO** has given a more comprehensive definition for drug: “**Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological status for the benefit of the recipients.**”

A single drug does not fulfill all the purposes, for example, BaSO_4 used for the diagnosis, Polio vaccine is used for prophylaxis of poliomyelitis, while metronidazole is commonly used for the treatment of amebiasis with the purpose to cure the disease.

SUBDIVISIONS OF PHARMACOLOGY

Pharmacokinetics: It is the scientific study of fate of the drug in the body including absorption, distribution, biotransformation, and excretion. In short it deals with “*what the body does to the drug*”.

Pharmacodynamics: It include the study of:

1. Biological effects of the drug.
2. Site and ‘mechanism of action’ of the drug.
3. ‘Dose: response’ relationship.

In short it deals with “*what a drug does to the body*”.

Pharmacy: It is the science of collection, identification, selection, purification, isolation, preservation, standardization, synthesis, quality control and dispensing of medicinal substances.

Pharmaceutics: It is the large-scale manufacturing of the drugs, and the company is called as Pharmaceutical Ltd.

Pharmacognosy: It is the study of the identification of sources of drugs and study of physical and chemical properties of such substances.

Therapeutics: It is the practical branch of medicine dealing with the science and art of the treatment of diseases.

Pharmacotherapeutics: It is the treatment of diseases by means of drugs. It utilizes information on drugs obtained by pharmacodynamic studies.

Empirical therapeutics: It is the therapy based on clinical evidence that the drug is effective even if the

mechanism of action of drug is unknown, i.e. during ancient time, chaulmoogra oil was used for the treatment of leprosy and mercurial compounds were for syphilis.

Chemotherapy: It is the treatment of systemic infection or malignancy with the drugs which are having selective toxicity for the infecting organisms/malignant cells with no or minimal effect on the host cells.

Chemotherapy has two components:

1. **Chemotherapeutic agents:** These are the substances, which kills or inhibits the invading microorganisms (malignant cells) with no or minimal pharmacodynamic effect in the recipient cells.
2. **Pharmacodynamic agents:** These are the substances having pharmacodynamic effects in recipient cells.

Toxicology: It is the branch of science, which deals with the study of untoward effects of any substance including drug toxicities or poisoning, whether because of internal or external exposure, and relating to both immediate and long-term implications in the realm of human ecology.

Clinical pharmacology: It is the scientific study of the effects of drugs in man. It provides information's regarding usefulness, efficacy, potency, toxicity and safety of new drugs in human (Patients).

Materia medica: It is the older term for a branch of pharmacology which concerned with the literature on sources, description and preparation of drugs.

Pharmacopoeia: It is an official monograph/compendia, containing a selected list of the established drugs, their chemical and structural formulae, solubility information, description, identification, purity data, direction for storage and dosages.

National formulary: These are the publication of different countries that included various informations on the products (formulations), available to prescribers in the respective countries. The national formulary is a smaller and much more handy book.

Recent Arrived Branches in the Pharmacology are:

Biotechnology: The branch of science which deals with the production of drugs, medicines and other useful products by biological means, i.e. by using recombinant DNA technology. (e.g. Production of antibiotics, hormones, etc. from microorganisms).

Pharmacogenetics: It is the branch of Pharmacology which deals with the study of genetic effect or influences

on responses to drugs. In other words it deals with the study of genetically determined variations in drug responses.

Pharmacogenomics: This is the branch of Pharmacology, which overlaps the Pharmacogenetics by definition. It deals with the study of choices of drug therapy in different individuals on the basis of available genetic informations.

Pharmacoepidemiology: Branch of Pharmacology which deals with the study of drugs in the society (at population level).

Pharmacoeconomics: This Pharmacological branch aims to quantify in economic terms the cost and benefit of drugs used therapeutically.

Pharmacovigilance: It includes detection, assessment understanding and prevention of adverse effects or any other drug related problems.

Drug Information Sources

Primary sources

- i. Original studies and reports in Journals.
- ii. Monographs.
- iii. Published conference proceedings and symposia.

Drug compendia

- i. Pharmacopoeias: Pharmacopoeia of India, British Pharmacopoeia, United State Pharmacopoeia, Extra Pharmacopoeia (Martindale), etc.
- ii. National Formularies.
- iii. Monthly Index of Medical Specialties: MIMS
- iv. Current Index of Medical Specialties: CIMS
- v. Physicians Desk Reference.
- vi. Advance Drug Review (ADR).

Books

- i. The Pharmacological basis of therapeutics: Goodman & Gillman.
- ii. Basic and Clinical Pharmacology: B.G. Katzung.
- iii. Pharmacology: H. Rang, M Dale and J Ritter.
- iv. Lippincott's Illustrated Pharmacology: R Harvey & P. Champe.
- v. Essential of Pharmacotherapeutics: F. Barar
- vi. Pharmacology and Pharmacotherapeutics: Satoskar, et al.
- vii. Essential of Medical Pharmacology: K. D. Tripathi.
- viii. Text book of Pharmacology: S. D. Seth
- ix. Clinical Pharmacology: Laurence et al.
- x. DRUG

Sources of Drugs, Nomenclature and Essential Drugs

SOURCES OF DRUGS

Drugs are mainly obtained from:

Plants: From roots, leaves, barks and fruits. Example; *quinine from cinchona bark, digitalis from fox-glow and atropine from datura, etc.*

Animals: Example; *insulin, thyroid powder, heparin, etc.*

Minerals: Example; *ferrous sulphate, magnesium trisilicate, iodine, phosphorous, gold, etc.*

Synthetic and semi-synthetic: They are prepared from chemical substances, or by altering the natural substances chemically. Examples; *sulphonamide, thiazide, sympathomimetics, etc.*

Recombinant DNA technology: Example; production of human insulin by introducing coded DNA into harmless strains of *E. coli*.

Microbiological: Example; Antibiotics like *penicillin, bacitracin, streptokinase, etc.*

NATURE OF DRUGS

Different drugs are grouped as per according to their physical and chemical properties, i.e.

Alkaloid: Composed of C, H, N, & O. They have bitter test and are usually poisonous, e.g. *caffeine, atropine, morphine, etc.*

Glycoside: They are sugars + other organic substances, i.e. usually glucose + aglycone. e.g. *digoxin, digitoxin, etc.*

Oils: They are the liquids which are insoluble in water and highly viscous. They are of three kinds:

- Volatile oil: They evaporates on heating, e.g. *clove oil, peppermint oil, oil of wintergreen, etc.*
- Fixed oils: They are the glycerides of oleic, palmitic and stearic acid. They do not evaporate

easily, e.g. *Olive oil, castor oil, cotton seed oil, peanut oil, etc.*

- Mineral oils: They are mixture of hydrocarbon obtained from petroleum, e.g. *hard paraffin, soft paraffin, liquid paraffin, etc.*

Tannins: They are non : nitrogenous, and having astringent action. They are of two type a) Pyrogallol tannins and b) pyrocatechol tannins, e.g. *tennic acid*.

Gums: They are polysaccharide exudates of plants and their hydrolysis yields sugar, e.g. *Methylcellulose, tragacanth, gum acacia*.

Resins: They are ill defined solid substances present in the plants, and are produced by oxidation and polymerization of volatile oils, e.g. *gum resins, balsams, etc.*

Antibiotics: They are the chemical substances which are produced by microorganism and are used for killing some other microorganisms (pathogenic), e.g. *Penicillin, streptomycin, etc.*

Hormones: These are the chemicals usually derived from animal endocrine gland or by DNA recombinant technology from *E. coli*. e.g. *Insulin, Thyroxin, etc.*

DRUG NOMENCLATURE

Individual drugs can be named in three different ways:

- Chemical name:** It describes chemical composition/ arrangement of atoms or atomic group in the drug, e.g. *Acetyl salicylic acid*.
- Official name:** The drug name approved officially by a authorized body and is same (common) all over the world and is also included in the official publication of the country (Pharmacopoeia), e.g. *Aspirin*.
- Proprietary name:** It is also called as trade or brand name. It is the name assigned to a drug by the manufacturer (patent drug), e.g. *Disprin, Ecosprin, etc.*

Note: Official name is also called non-proprietary name.

Chemical Name : Acetyl Salicylic Acid
Official Name : Aspirin
Proprietary Name : Disprin, Ecosprin, etc.

Chemical Name : P-Acetamino Phenol
Official Name : Paracetamol
Proprietary Name : Crocin^R

Drug Categories

Non-prescription drugs: These are comparatively safer drugs and are sold **over the counter [OTC]**.

Prescription drugs: These drugs should be used under medical supervision only and are therefore prescribed by registered medical practitioners.

Orphan drug: Orphan drugs are the drugs, which are meant for the diagnosis, prevention and treatment of certain rarely occurring diseases like certain anti-cancerous drugs, certain anti-virus drugs, pentamidine, etc.

ESSENTIAL DRUGS

The **WHO** has defined “**Essential Drugs**” as those that satisfy the health care needs of **majority of population**; they should therefore be **available at all times** in adequate amounts and in appropriate dosage forms.

The **WHO** has laid down criteria to guide selection of essential drugs—

- Adequate data on its efficacy and safety should be available from clinical studies.
- Good dosage form ensuring proper bioavailability, stability and quality should be available.
- Its choice should depend upon pattern of prevalent diseases.
- In case of two or more similar drugs, choice should be made based on their relative efficacy, safety, quality, price and availability. Cost-benefit ratio should be a major consideration.
- Most essential drugs should be single compounds. Fixed ratio combinations should generally be avoided.
- Selection of essential drugs should be a continuous process.

WHO publishes model list of essential drugs and currently 11th revision (1999) is available. Govt. of India has published its National Essential Drugs List in 1996. Only 279 drugs have been included in this. Some examples:

- Analgesic/Antipyretic drugs included in National essential drugs list:** Acetyl Salicylic Acid (Aspirin), Diclofenac, Ibuprofen, Paracetamol. (Indomethacin is included in WHO list. NOT in India).
- Antihypertensives included in National essential drugs list:** Amlodipine, Atenolol, Captopril, Diltiazem, Enalapril, Hydrochlorothiazide, Methyldopa, Nifedipine, Propranolol, Sodium nitroprusside, Verapamil. (Reserpine is included in WHO list. NOT in India). **Such lists greatly facilitate rational prescribing.**

New Drug Discovery and Development

INTRODUCTION

Drugs have become one of the important needs of human being. Before any new drug is introduced in the market or a new treatment modality (different routes, doses, frequency, duration of established drug or new therapeutic procedure) is used in human beings, it has to pass through several stages of development.

Bringing (discovering) one new drug in the market typically costs a pharmaceutical or biotechnology company nearly \$900 million and takes an average of 10 to 12 years.

WHY NEW DRUGS

Large number of drugs exist today, then what is the need of new drug? Answer is:

- i. Because of orphan area (no drugs available for rarely occurring diseases).
- ii. Drugs are available but are very toxic (anticancer).
- iii. Curiosity
- iv. Problem with Pharmacokinetics (need of oral insulin therapy).
- v. To establish the value of an existing drug for new uses.
- vi. To compare the new drug (efficacy) with pre-existing drug (may be more efficacious).
- vii. To check the safety of a new compound (may be less toxic).

SOURCES OF DRUGS

Discussed in previous chapter.

HOW NEW DRUGS DISCOVERED ?

New drugs begin in the laboratory with chemists, scientists and Pharmacologists who identify cellular and genetic factors that play a role in specific diseases. They search for chemical and biological substances that target these biological markers and are likely to have drug-like effects. Animal (pre-clinical) studies are usually carried out first to

establish efficacy and safety, this is followed by carefully planned studies on human beings. Out of every 5,000 new compounds identified during the discovery process, only five are considered safe for testing in human volunteers after preclinical evaluations. After three to six years of further clinical testing in patients, only one of these compounds is ultimately approved as a marketed drug for treatment. The following sequence of research activities begins the process that results in development of new medicines. Different phases of these preclinical and clinical trials are discussed in Table 1.3.1.

New medicines are developed as follows:

Animal experiments or preclinical studies: It is the first step towards developing a new drug. A pharmaceutical company or Research Institute conducts laboratory and animal studies to show biological activity of the compound against the targeted disease, and the compound is evaluated for safety.

Animal experiments are carried out to:

- Establish the actions of a potentially useful compounds.
- Further study the actions of established drugs
- Establish the safety of the drugs : toxicological studies
- Establish pharmacokinetic properties of the drugs
- Have an estimate about the dose required
- Study drug interactions, etc.

During the preclinical development of a drug, laboratory tests document the effect of the investigational drug in living organisms (*in vivo*) and in cells in the test tube (*in vitro*).

- 1. *In vitro* experiments:** They are carried out on isolated organs or tissues or cells. Tissues or the organs are taken out of the body and are maintained under physiological conditions.
- 2. *In vivo* experiments:** They are carried out on live, intact animals. These studies are useful in observing the response to a drug under the influence of several systems of the body.

Table 1.3.1: Phases of preclinical and clinical trials

Clinical Trials									
	Preclinical testing	File IND at FDA	Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5		1	2	3		2.5	12 Total	
Test population	Laboratory & animal studies		20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers	File IND at FDA	Reveiw process / Approval		Additional Post-marketing testing required by FDA
Purpose	Assess safety & biological activity		Determine safety & dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use				
Success rate	5,000 compounds evaluated		5 enter trials						

Pharmacology/Toxicology: Pharmacological testing determines effects of the candidate drug on the body. Toxicology studies are conducted to identify potential risks to humans, these includes acute, subacute, and chronic toxicity testing and other specific studies like carcinogenicity, mutagenicity and teratogenicity, etc.

Investigational new drug application (IND): After completing preclinical testing, the company files an IND with FDA [**Food and Drug administration**] to begin to test the drug in people. In India the governing body is “**Drug Controller of India**” The IND becomes effective if FDA does not disapprove it within 30 days. The IND shows results of previous experiments, how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. In addition, the IND must be reviewed and approved by the **Institutional Review Board** where, the studies will be conducted, and progress reports on clinical trials must be submitted at least annually to FDA.

Investigational drugs in human (Clinical Trial): The goal of clinical trials is to determine (evaluate) efficacy and safety of new drug. All research should begin with a basic ethical question: “**Do the potential benefits outweigh the potential harm?**” Researchers design trials that allow them to learn as much as possible about a new treatment or medication in ways that minimize the risk of injury to participants. Therapies that prove effective during trials may become the new standard of treatment for a condition. Comparing similar groups of people taking different treatments for the same type and stage of disease indicates that

any benefits are due to the treatment rather than to chance or other factors.

The ethics related to clinical trial

- 1. The objective:** Must be that, no patient should be worse off than they might have been in the hands of a reasonable and competent physician.
- 2. The right to choose:** People have the right to choose for themselves whether or not they will participate in the trial.
- 3. Injury to research subject:** WHO guideline state— Research subjects who suffer physical injury as a result of their participation are entitled to such financial or other assistance that can compensate them equally for any temporary or permanent impairment or disability. In the event of death their dependents are entitled to compensation.

Phases of Clinical Trials

Clinical testing is usually described as consisting of Phase I, Phase II and Phase III clinical studies. In each successive phase, increasing numbers of patients are tested.

Phase I Clinical Studies: These are the first studies conducted in humans. Phase I studies are open studies and designed to verify safety and tolerability of the candidate drug in humans and typically take six to nine months. A small number of subjects, usually from 20 to 100 healthy volunteers, take the investigational drug for short periods of time. Testing includes observation and careful documentation of how the drug acts in the body — how it is absorbed, distributed, metabolized and excreted, how much of the treatment to give, how the human body react to the treatment, how much can be given safely, the best way to give the treatment, any harmful effect, etc.

Phase II Clinical Studies [Clinical Investigation]:

Phase II studies are designed to determine effectiveness and further study the safety of the candidate drug in humans and establishes the minimum and maximum effective dose. This phase of development generally takes from six months up to three years. Testing is conducted with up to several hundred patients suffering from the condition. Most Phase II clinical trials are randomized, or randomly divided into groups, one of which receives the investigational drug, while other group gets a placebo containing no medication and sometimes a third that receives a current standard treatment to which the new investigational drug will be compared. In addition, most Phase II studies are double-blinded, meaning that neither patients nor researchers know who is receiving the investigational drug or who is receiving placebo.

Phase III Clinical Studies [Formal Therapeutic Trial]:

Phase III studies provide expanded testing of effectiveness and safety of an investigational drug, usually in randomized and blinded clinical trials. Depending upon the type of drug candidate and the condition it treats, this phase usually requires one to four years of testing. Phase III, clinical trial is conducted with several hundred to thousands of volunteer patients suffering from the condition the investigational drug treats.

New Drug Application (NDA)/Marketing Authorization Application (MAA)

NDAs (in the U.S.) and MAAs (in the U.K.) are examples of applications to market a new drug. Such applications document safety and efficacy of the investigational drug and contain all the information collected during the drug development process. At the conclusion of successful pre-clinical and clinical testing, this series of documents is submitted to the FDA in the U.S. or to the applicable regulatory authorities in other countries. The application must present substantial evidence that the drug will have the effect it is represented to have when people use it or under the conditions for which it is prescribed, recommended or suggested in the labeling. Obtaining approval to market a new drug frequently takes between six months and two year.

After the FDA (or other regulatory agency for drugs marketed outside the U.S.) approves a new drug, pharmaceutical companies may conduct additional studies, including Phase IIIb and Phase IV studies. Late-stage drug development studies of approved, marketed drugs may continue for several months to several years.

New Drug Application (NDA): Following the completion of all three phases of clinical trials, the company

analyzes all of the data and files an NDA with FDA if the data successfully demonstrate safety and effectiveness. The NDA must contain all of the scientific information that the company has gathered. NDAs typically run 100,000 pages or more. By law, FDA is allowed six months to review an NDA. In almost all cases, the period between the first submission of an NDA and final FDA approval exceeds that limit; the average NDA review time for new molecular entities approved in 1992 was 29.9 months.

Approval: Once FDA approves the NDA, the new medicine becomes available for physicians to prescribe. The company must continue to submit periodic reports to FDA, including any cases of adverse reactions and appropriate quality-control records. For some medicines, FDA requires additional studies (Phase IV) to evaluate long-term effects.

Discovering and developing safe and effective new medicines is a long, difficult and expensive process. The research-based pharmaceutical industry will invest \$12.6 billion in research and development per year, and that investment has been doubling every five years.

Phase IV Studies & Post-Market Studies: Post-market studies test a marketed drug in new age groups or patient types. This is ongoing open ended study. Some studies focus on previously unknown side effects or related risk factors (i.e. nimesulides). As with all stages of drug development testing, the purpose is to ensure the safety and effectiveness of marketed drugs. During this phase pattern of drug utilization and additional indications are also discovered.

STUDY DESIGNING

- 1. Prospective study:** It is a planned study, where effects are recorded after administering the drug and then studied. Most of the clinical trials are prospective studies.
- 2. Retrospective study:** In this study, the data available from earlier record or study or trial are analyzed and then studied.
- 3. Open study:** In this type of study, one group receives the "New Drug" & its effects are recorded. This may be compared with an another group, which does not receive anything. Subject is open to all.
- 4. Parallel group:** In this case each group receives a different treatment, with both groups being entered at the same time. In this case, result are analyzed by comparing groups.

5. **Paired group:** Subject receiving different treatments are matched to balance potential confounding variables such as age and sex. Results are analyzed in terms of differences between subject pair.
6. **Single blind:** In this type of study subject did not know which treatment they receiving.
7. **Double blind:** Neither investigator nor subjects knew who was receiving which treatment.
8. **Crossover study:** In this type of study each subject received both the intervention and control treatments (in random order) often separated by a washout period on no treatment.
9. **Placebo controlled:** Control subjects receive a placebo (inactive drug tablet), which should look and taste the same as the active drug tablet. Placebo (sham) operation may also be used in trial of surgery.

Routes of Drug Administration

Drugs can be administered in the patients by various routes. The option of the route of drug administration in a particular patient depends upon the characteristic properties of the drug and convenience to the patient. Therefore a sound knowledge, regarding the advantages and disadvantages of the different routes of administration of the drug is essential. Various factors that govern the route of drug administration are mention below:

The routes of the drug administration can be broadly divided into:

A. Local (Topical) Application

1. For local action
2. For systemic action

B. Oral (Gastrointestinal or enteral) Route

C. Parenteral Routes

1. **Injections:** Intradermal, subcutaneous, intramuscular, intravenous, intra-articular, intrathecal, intra-arterial, intraperitoneal.
2. **Inhalation:** MDI, MDI with spacer, Nebulizer, Spinhaler, Boyle's apparatus.
3. **Sublingual**

D. Newer Methods of Drug Delivery

1. Transdermal skin patches (nitroglycerine, hyoscine).
2. Ocusert (pilocarpine), progestasert (progestin).
3. Prodrugs (levodopa, bacampicillin).
4. Subcutaneous implants (contraceptives).
5. Targeted delivery systems: For anti-cancer drugs.
6. Slow/sustained release preparations (nifedipine, isosorbide dinitrate).
7. Others: Insulin pump, jet injections, etc.

Note: This classification is not fixed or uniform—there are many instances of overlapping.

FACTORS DECIDING ROUTES OF ADMINISTRATION

Decision regarding route of administration of a drug is very important. Following factors help in deciding routs of drug administration:

Action of the Drug: A drug like MgSO_4 produces different actions when given by different routes. Chances of gastric irritation are remote when a drug is given by parenteral route. Dose requirement may also differ between oral and parenteral routes. Peak plasma concentration is usually achieved more rapidly with parenteral routes.

Onset of Action: Usually, the onset of action is slower with oral administration as compared to parenteral. A drug given intravenously will have rapid onset of action and will produce higher plasma concentration (and some times therefore more toxic effects).

Convenience: Oral route is undoubtedly the most convenient route for drug administration and hence is the most preferred route. However, in seriously ill or unconscious patients or in children, oral administration may be less convenient or not possible at all.

Cost: Cost is another very important factor affecting selection of a route of administration. The parenteral preparations are not only more costly to purchase, the total cost increases further because of the requirement of aseptic precautions and the need for trained personnel (e.g. nurse or a doctor) for administration (usually self administration is not possible for injectable preparations).

- **Rate and extent of absorption of the drug from different routes of administration.**
- **Physical and chemical properties of the drug, i.e. whether the drug is solid/liquid/gas/irritant or non-irritant, etc.**

- **Amount of drug:** Any route can be used for a small amount, a moderate amount is given by oral route, but very large amount, within a short period needs IV route.
- **Sites where the action of the drug is required, i.e. local, general or non-approachable.**
- **Patient related factors:** Whether patient is conscious or unconscious, patient has vomiting or not.

LOCAL ROUTES

Topical: Topical application means the application of the drugs to skin and mucous membrane for local effects, e.g.

Lotion	Liquid preparations meant for application on the skin and mucous membrane (soluble/insoluble ingredients). Used for soothing and cooling effect.
Liniment	Alcoholic or oleaginous solutions or emulsions for external application with rubbing. They are for irritant and counter-irritant actions.
Paints	Viscid preparation meant for local application.
Ointment	For local action, for systemic action—mixture of drug in ointment base.
Creams	Semisolid emulsions, generally less viscid and lighter than ointments.
Jelly	(Medicated/non-medicated). Easier to introduce into body cavities than ointment or cream.
Paste	Contain more solid materials, are stiffer and less penetrating
Plasters	Solid or semisolid adhesive masses spread upon a backing material—for external application.
Suppositories (rectal-vaginal-urethral)	These are solid dosage forms intended for insertion into body orifices where they melt, soften or dissolve and exert local or systemic effects
Pessaries	Vaginal suppositories
Bougies	Urethral suppositories
Ocuserts	Placed under eye-lids for continuous release of drug

Deeper tissues

- Articular (joints) Injection: Corticosteroid (in arthritis).
- Retrobulbar (eyes) Injection: Corticosteroid acetate.
- Intrathecal (subdural) Injection: Lignocaine.
- Intramedullary (in bone marrow): Anticancerous, etc.

Arterial

- Coronary artery: Contrast media for angiography
- Intra-femoral or intra-bracheal: Anticancerous drugs.

Sometime drugs may be applied locally to obtain systemic action, e.g.

Hyoscine patch	For motion sickness
Nitroglycerine patch	In angina
ADH spray	Diabetes insipidus
Nicotine patch	De-addiction program, etc.

SYSTEMIC ROUTES

- Oral (Enteral routes):** It is the oldest, safest and commonest route of drug administration
Effective barrier – Epithelial lining of the GIT.

Advantages of oral route of administration

- Complications of parenteral therapy are avoided.
- Safe
- Convenient
- Economical
- No assistant is required (self administration is possible).

Disadvantages

- Oral route is not useful in the patients who are vomiting, unconscious or non-cooperative.
- Irritant and unpalatable drugs cannot be administered orally.
- Some drugs are destroyed by gastric HCL (e.g. penicillin) or by digestive enzyme (e.g. insulin)
- Some drugs undergo extensive first pass metabolism in the liver, e.g. (Lidocaine and nitroglycerine).
- Highly polar compounds are not absorbed orally.

Drug formulations for oral routes

Liquids	
Aqueous	Waters (simple, medicated, aromatic), gargles and mixture.
Syrup	Simple, medicated, aromatic or flavored solutions.
Tincture	Alcoholic solutions
Extracts	Concentrated preparations of vegetable or animal origin
Linctus	Viscous, oral preparation usually employed for cough
Drops	Pediatric drops. Drop size is variable.

Emulsion	Oily ingredient made miscible with water
Mixture	liquid formulations meant for internal use are defined as mixtures.

Solids

Powders, Granules, Pellets, Pills, Tablets, Capsules, Spansules, Lozenges, Pearls, Kapseals, Applicap, etc.

Tablets Plain, scored, sugar coated, enteric coated, sustained release, sublingual, chewable.

Lozenges Dissolve slowly in oral cavity and produce local effect.

Oral Route: Some Newer Preparations

Slow/Sustained Release (SR) Preparations: With certain drugs, frequent (2 - 3 - 4 times a day) administration is required. This may be inconvenient for the patient. SR preparations release the drug slowly and steadily over a longer period. With such preparations, the peak plasma concentration of the drug will be lower, but the action will continue for a longer period. In such a case, the extent (%) of absorption will be less. Examples: *Isosorbide dinitrate (ISOMACK RETARD*)*, *Nifedipine (CALCI-GARD RETARD*)* (Names in CAPITALS = Proprietary/Trade names)

Spansules: These are the preparations containing granules. These granules are coated with different coatings. When the outer coating dissolves in the GIT, granules are released. As the granules are coated differently, the drug will be released from various granules at different times. This will result in slow release of small quantities of drug over a longer period.

Example: Ferrous sulphate spansules (FEFOL).

Enteric Coated Tablets: Certain drugs (e.g. erythromycin) are destroyed by the gastric acid. As the drug is absorbed from the small intestine, it is necessary to deliver the drug into the small intestine. For this purpose, the tablet is coated with acid resistant material which will permit passage of intact tablet into the small intestine.

2. Parenteral: As the name itself suggests (par: other, enteral: intestinal) i.e. any route other than the enteral route of administration. In this case the drugs are directly poured or delivered into the blood or into tissue fluids.

Advantages

- This route can be used in either an uncooperative patient or in an unconscious patient.

- First pass metabolism is bypassed.
- Action of the drug is more rapid and predictable.
- The drugs, which are considered to be irritants, are administered directly into the blood through (parenteral route) it.
- This route is also a preferable route.

Disadvantages

- Pain at the site of injection.
- Asepsis must be maintained.
- Inconvenient route.
- Very expensive, and unsafe.
- Injury to surrounding tissues, vessels or nerve may occur.

A. Drug Administration by Injections

Injecting by different routes

I. Intradermal: In this procedure the drug is injected into the layers of the skin (dermis) raising a bleb, e.g. BCG vaccine, tests for the allergy or by multiple punctures of the epidermis, i.e. small pox vaccine. It is a painful procedure and only small amount of the drug is administered through this route.

II. Subcutaneous (SC): The drug is deposited in the subcutaneous tissue. The SC tissue is less vascular. The absorption of the drugs occurs very slowly and uniformly, making the drug long acting. Self-administration is possible in this route. Common sites for subcutaneous injections are the outer surface of the upper arm, abdomen, and front of the thigh. Drugs like adrenaline, morphine and insulin are usually administered through this route.

Disadvantages

- Irritant drugs cannot be administered because SC tissue is highly supplied by nerve fibers as a result they are painful and may cause tissue necrosis.
- Repeated administration at the same site can cause lipodystrophy, which also affect normal absorption.
- This route is used to inject a small amount of the drug (2 ml or lesser) only not larger volume.

Hypodermoclysis: It is a form of subcutaneous injection in which large amounts (500 to 1000 ml in adult) of fluid such as normal saline or 5% dextrose is slowly administered in the patients. It is extremely beneficial for infant and children to treat dehydration. Special precaution should be kept to prevent too rapid injection, which in otherwise causes circulatory overload on the heart.

Dermojet injection: It is a painless and needle less injection of the drug which is administered by means of a high velocity jet projected through a micro fined

orifice using a gun. The drug gets deposited in the subcutaneous tissue beneath the skin from where it is absorbed. Generally vaccines are administered through this route.

Pellet and biodegradable (sialistic) implants: In this procedure the drugs are pellet or packed in biodegradable or sialistic tubes and are implanted subcutaneously beneath the skin to provide a slow but uniform release of the drug and for long lasting effect.

III. Intramuscular (IM)

Sites and procedures for IM drug administration

Procedure: The drug is injected into one of the mentioned muscles. These muscles are rich in blood supply; therefore absorption is rapid and uniform.

Deltoid Muscle, Gluteal Muscle

Deep IM: Particularly for irritant and painful drugs (e.g. benzathine penicillin)

Z-technique: Particularly to avoid staining of skin (e.g. iron).

Injection can be given in **Vastus lateralis** muscle also.

Advantages

- Absorption is more predictable and less variable.
- Absorption is also rapid compared to oral route and
- Mild irritant, suspensions and depot preparations can also be given by this route, for obtaining sustained effect.

Disadvantages

- Perfect aseptic precautions are required.
- Chances of abscess development at the site of injection.
- Comparatively procedure is painful.
- Chances of nerve damage due to irritant drugs may lead to paresis of the muscle, supplied by it and
- Large volumes of the drug cannot be administered (not more than 10 ml).

IV. Intravenous (IV)

In this procedure, the drug is directly injected into the vicinity of superficial vein so that the drug reaches directly into the circulation and is immediately available for the action.

Procedures

- Bolus Injection: an initial large (bolus) dose is given.
- Rapid i.v. Injection; just like normal injections and
- Slow i.v. Injection given over 10 – 15 minutes or
- I.V. infusion: Injection given over 1 to 8 or more hours.

Sites: Cubital fossa, anterior aspect of forearm and the dorsum of hands, medial surface of ankle.

Advantages

- As the drug enters the systemic circulation directly, the first pass effect get bypassed, there is a quick onset of action and a lesser dose is required to achieve the desired plasma state concentration.
- As per the need of response doses can be adjusted. Rapid dose adjustment is possible in case of development of any adverse effect.
- Useful during emergent conditions.
- Can be employed even in unconscious and uncooperative patients.
- Large volume of the drugs can be administered (infused)
- Irritant drugs (e.g. chloroquine) can be administered.

Disadvantages

- Strict aseptic precaution is required.
- Patient has to depend upon the second person for taking injection.
- Irritant drugs may causes thrombophlebitis (inflammation and necrosis) or venous thrombosis of the vein.
- Depot preparations and suspensions cannot be administered through this route.
- Once the drug is injected it cannot be withdrawn (recalled).

V. Intraperitoneal administration: In this route of administration, drug is administered into the peritoneal cavity, e.g. antirabies injections, injections used for peritoneal dialysis. Generally it is the most commonest route of administration of drugs in animals.

Advantage: Rapid absorption of the drug occurs due to larger surface area.

Disadvantages

- Painful
- More risky due to chances of infections and inflammations (adhesions) in peritoneal cavity (peritonitis).

VI. Intrathecal (Intraspinal) administration: It is the administration of the drug into the subarachnoid space of the spinal cord, e.g. Local anesthetic agents like benzocaine for spinal anesthesia, radiopaque contrast media for myelography (to visualize spinal cord) and certain antimicrobial agents to treat infectious meningitis.

Advantages

- Blood brain barrier and blood CSF barrier are bypassed.
- Significant CSF concentration of the drugs are provided.
- Drugs act directly on the meninges and CNS.

Disadvantages

- i. Painful
- ii. Headache, nausea and vomiting are always associated.
- iii. High chances of infection is there (strict aseptic precautions are needed).
- iv. It is a risky procedure therefore a great expertise is needed. (Otherwise chances of damage and injury to spinal cord is there).

VII. Intramedullary administration: Simply administration of the drug into bone marrow. Generally tibial and sternal bone marrow is the commonest site for administration. Example includes bone marrow transplantation, sometime blood is also transfused in special conditions.

Advantages

- i. Fulfillment of special need and requirement.
- ii. Onset of action is fast.

Disadvantages

- i. Painful.
- ii. High chances of infections are there (strict aseptic precautions are needed).
- iii. It is again a risky procedure therefore a great expertise is needed.

VIII. Intra-arterial administration: During this procedure, drug is administered into the lumen of specific (desired) artery, e.g. nitrogen mustard is administered in the lumen of peripheral artery to treat cancer involving limbs. Radiopaque contrast media is administered in coronary and cerebral artery for investigational purpose.

Advantage: Higher concentration of the drug can be delivered at the specific site of action.

Disadvantages

- i. High chances of infections are there (strict aseptic precautions are needed).
- ii. It is again a risky procedure therefore a great expertise is needed.

IX. Intra-articular injections: In this procedure drug is directly injected into the articular space (joint space) e.g. hydrocortisone or gold chloride injection for the treatment of osteoarthritis or rheumatoid arthritis.

Advantage: Higher concentration of the drug can be delivered at the specific site of the action, i.e. (articular space)

Disadvantages

- i. Highly painful procedure.
- ii. Repeated administration of the drug by repeated puncturing the joint cavity (space) may further damage the joint.

- iii. High chances of infections are there (strict aseptic precautions are needed).
- iv. It is again a risky procedure therefore a great expertise is needed.

B. Transdermal Patches

In this procedure, a patch [adhesive matrix containing specific drug] is applied to the skin on chest, abdomen or mastoid region, e.g. Hyoscine/scopolamine (for motion sickness), Nitroglycerine (for angina), and clonidine (for hypertension) transdermal patches for systemic effect.

Advantage: Through this route there occurs slow but sustained release of the drug for several hours.

Disadvantage: Not specific, but if irritation occurs, requires change in the application site.

C. Sublingual

In this route of administration, a tablet-containing medication is placed under the tongue or crushed in mouth and spread over the buccal mucosa for quick absorption. Absorption occurs through lingual vein to superior vena cava, e.g. nitroglycerine in angina, nifedipine in hypertensive emergencies, etc.

Advantages

- i. If tablet is chewed, quick onset of action (effect).
- ii. The effect of the tablet (drug) can be terminated just by spitting out the tablet.
- iii. First pass metabolism is bypassed.

Disadvantages

- i. Inconvenience.
- ii. Irritation of the mucous membrane (ulceration).
- iii. Excessive salivation.
- iv. Excessive swallowing (loss of bypassing first pass metabolism).

D. Rectal

The mucosa of the rectum has a rich blood and lymph supply and therefore drugs can be administered through this route. The dose requirement is either the same or slightly higher as compared to oral route. If absorption occurs from upper part of rectum, the drug is carried to portal circulation through superior hemorrhoidal veins, while that absorbed from the lower part of the rectum is carried to the systemic circulation through middle and inferior hemorrhoidal veins. Paraldehyde, diazepam, indomethacin and chlorpromazine like drugs can be administered per rectally.

Advantages

- i. Irritant drugs can be administered.
- ii. This route is highly beneficial during; vomiting, migraine, motion sickness, or when patient is not able to swallow.
- iii. Can also be administered by unskilled person.

Disadvantages

- i. Patient inconvenience (embarrassment)
- ii. On repeated administration, rectal inflammation can occur.
- iii. Absorption may be unreliable and unpredictable (especially if the rectum is full of feces).

Drugs can also be given as **enema** by this route:

Enema can be defined as per rectum administration of the drugs in the liquid form. It is of two type a) Retention enema and b) Evacuant enema.

- a. **Retention enema:** In this procedure, the drug is administered with approximately 100 to 200 ml of the fluid and is retained in the rectum for its local action, e.g. prednisolone.
- b. **Evacuant enema:** In order to evacuate the rectum, large volume of the fluid (about 600–700 ml of soap water) is administered per rectally especially during or before surgical or obstetrical procedures and during examination of the rectum.

E. Inhalational

Inhalation can be given:

- i. As a gas: Volatile liquids, e.g. General anesthesia
- ii. As an aerosol: They are the particles dispersed in gas; the particles may be liquid (fog) or solid (smoke), but should be small enough to remain in the suspension for the long time.
- iii. As a powder: Particles of above $2\ \mu\text{m}$ reaches the terminal bronchioles, e.g. sodium chromoglycate.

Advantages

- i. Drugs as gases are rapidly taken up or eliminated.
- ii. Instantaneous absorption of a drug is achieved.
- iii. Self administration is possible.
- iv. First pass metabolism is avoided.
- v. Provide high local concentration for action on bronchi.

Disadvantages

- i. Special instrument is required for administration.
- ii. If patient is conscious, the drug must be non-irritant.
- iii. Irritant gases may enhance pulmonary secretions.

Inhaler, Spacer, Nebulizer: *Metered Dose Inhaler (MDI):* When the canister is pressed, a fixed quantity of the drug is released in an aerosol form.

- i. For its effective use, training in the form of synchronization between the release of the drug (pressing the button) and inspiration is required. There are chances of the drug particles sticking in the oral cavity if proper technique is not used.
- ii. The advantage of this drug delivery system is that the drug reaches directly at the site of action, i.e. the bronchial tree and very little amount of the drug enters the systemic circulation. Thus the onset of action is quick and systemic side effects are less.
- iii. The method is not costlier than oral tablets.

Spacer

- i. Spacer is used to overcome some of the drawbacks of the Inhaler. When the button of the inhaler is pressed, the drug is released in the chamber of the spacer from which the patient can inhale it. Strict synchronization between release of the drug and inhalation is not necessary.
- ii. Ensures better drug delivery. Particularly useful in children.

Spinhaler - Rotohaler - Rotacap: Device for delivering microfinned powder by inspiratory efforts of the patient.

Nebulizer

- i. It is a device that generates very fine particles (0.3 to 5 microns) of liquid in gas of uniform particle size.
- ii. Current of air or oxygen is passed through the drug.
- iii. It is effective even when the ventilation of the patient is impaired.

Pharmacokinetics

DEFINITION

Pharmacokinetics is a branch of Pharmacology that deals with absorption, distribution, metabolism and excretion of drugs. In other words, **'What a Body does to the Drug'** is studied in Pharmacokinetics.

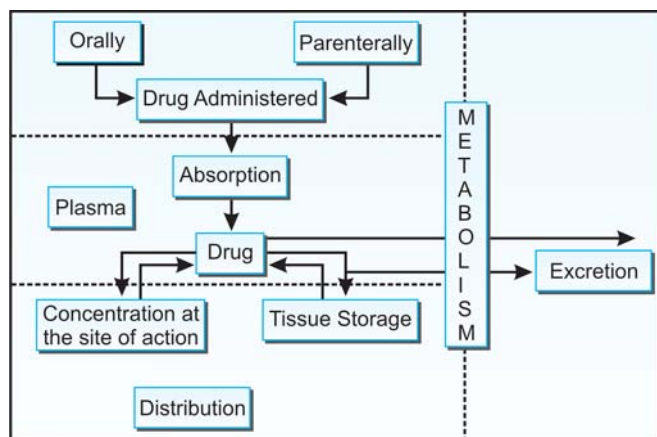


Fig. 1.5.1: Diagram showing pharmacokinetic process

All Pharmacokinetic processes specially bio-disposition of a drug involves transport of the drug across biological membrane.

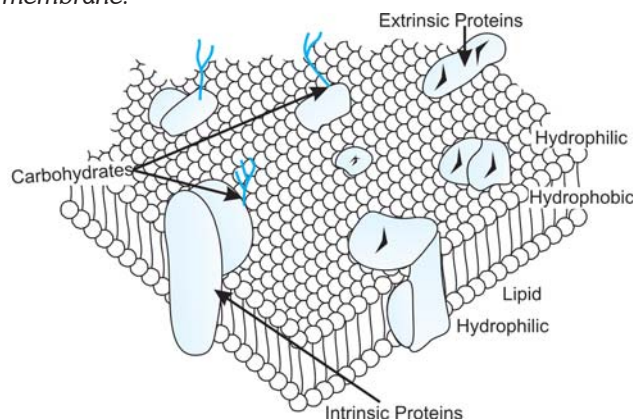


Fig. 1.5.2: Organization of a biological membrane

Overall, the transfer of the drug from the site of administration into the blood is called as **absorption** and its transfer from the blood into the tissue as **distribution**. The drug attains effective concentration at its site of action and so the onset of the drug effect. Then the drug is metabolized called as **biotransformation** and then thrown out of the body called as **excretion**. The relative rates of all these four process, taken together are called as **Pharmacokinetics** (Fig. 1.5.1).

BIOLOGICAL MEMBRANE

This is a bilayer of phospholipid (100 Å thick) and adsorbed protein molecules. The protein molecules are of two types: a) extrinsic proteins which are able to float freely through the membrane, and b) intrinsic protein molecules extended through the full thickness of the membrane, surrounding fine aqueous pores. Paracellular space/chamber also exist between the cells (epithelium/endothelium) as shown in (Fig. 1.5.2).

Drug permeation(transport) is dependent on

- Concentration Gradient.
- Surface area and vascularity.
- Molecular size and charge.
- Partition coefficient.

Partition Coefficient: It is the ratio of lipid solubility to aqueous solubility. The higher the partition coefficient, the more membrane soluble is the substance.

Kidney Glomeruli have the largest pores through which drugs can pass → drug filtration.

Blood Brain Barrier (BBB): Only lipid-soluble compounds get through the BBB.

Four peculiarities of Blood Brain Barrier:

- Tight Junctions in brain capillaries.
- Glial cell **foot processes** wrap around the capillaries.

- iii. Low CSF protein concentration → no oncotic pressure for reabsorbing protein out of the plasma.
- iv. Endothelial cells in the brain contain enzymes that metabolize, neutralize, many drugs before they access the CSF.

MAO and COMT are found in brain endothelial cells. They metabolize **Dopamine** before it reaches the CSF, thus we must give L-DOPA in order to get dopamine to the CSF.

Exceptions to the BBB: Certain parts of the brain are not protected by the BBB:

- i. Pituitary and Median Eminence
- ii. Supraventricular areas and
- iii. Parts of hypothalamus

Meningitis: It opens up the Blood Brain Barrier, due to edema. Thus Penicillin-G can be used to treat meningitis, despite the fact that it does not normally cross the BBB.

Penicillin-G is also actively pumped back out of the brain once it has crossed the BBB.

PASSIVE DIFFUSION

The driving force is – concentration gradient across biological membrane separating two body compartments:

- i. It does not involve a carrier and is not saturable and shows a low structural specificity.
- ii. This is very important mechanism for majority of drugs.
- iii. **Lipid soluble drugs** readily move across most biological membranes.
- iv. Whereas, **water-soluble drugs** penetrate the cell membrane through aqueous channels (pores).

Simple diffusion: Simple diffusion is based on **Fick's law**:

$$dQ/dt = (-D)(A)(dc/dx)$$

dQ/dt is the rate of drug efflux, i.e. (the change in concentration of a drug within a given time), **D** is a temperature dependent diffusion constant of the molecule, **A** is the area of the absorbing surface and **dc/dx** is the concentration gradient.

- i. The greater the concentration gradient, greater be the rate of absorption.
- ii. The larger the absorbing surface, greater be the absorption.
- iii. The “diffusion constant” **D** is directly proportional to temperature and inversely proportional to molecular size.
- iv. Greater be the partition coefficient, greater be the lipid solubility and therefore greater be the absorption of the drug.

Effect of pH on drug absorption: In simple diffusion, molecules cross the lipid membrane in an unionized (uncharged) form and it is a function of the **pKa*** of the drug and the pH of the medium and is expressed by the **Henderson-Hasselbach's equation**:

$$\text{Log} \frac{\text{base}}{\text{acid}} = \text{pH} - \text{pKa}$$

Henderson-Hasselbach's Equation

Weak Acid

pKa

- i. If its **pKa < pH** of the environment, then the conjugate base (anion) form of the species will predominate. Example = **CH₃COO⁻**
- ii. If its **pKa > pH** of the environment, then the environment is more acidic, so its acidic (neutral) form will predominate. Example **CH₃COOH**

Weak acids tend to be absorbed in acidic environments, like the stomach. They ionize more at alkaline pH, e.g. *Aspirin*.

Weak Base

pKa

- i. If its **pKa < pH** of the environment, then the environment is more basic, so the species will remain in the neutral form. Example = **NH₃**.
- ii. If its **pKa > pH** of the environment, then the environment is more acidic, so it will give up its extra H⁺ to the base, and the base will exist in its cation form. Example = **NH₄⁺**.

Weak bases tend to be absorbed in basic environments, like the duodenum (intestine). They ionize more at acidic pH, e.g. *atropine*, *morphine*, etc. (most of the commonly used drugs are weak bases).

Clinical importance of this consideration

- 1. Acidification of urine:** Increases ionization of weak base—ultimately increases their renal elimination, therefore overdosing of amphetamine and atropine can be treated by applying this principle.
- 2. Alkalization of urine:** It increases ionization of weak acid—increases their renal elimination; therefore this principle is used in the treatment of aspirin poisoning.

Filtration: It is the passage or bulk flow of drugs (solvent or solute) through aqueous pores (channels) in the membrane or through Paracellular space, because of pressure gradient.

- i. Majority of cells have very small size pores, i.e. intestinal mucosa has pore size of about (4 Å) and the drugs with molecular weight < 100 can pass through these pores (channels) very easily, while the drugs with molecular

weight > 100 – 200 are not able to penetrate them and can be filtered through intracellular or para cellular channels (Fig. 1.5.3).

- ii. However, capillaries (Except Blood Brain Barrier) have large pores size (40 Å) and therefore most drugs and even albumin can filter through these capillaries.
- iii. Concentration gradient also affect the rate of filtration.

Carrier mediated transport: The drug combines with a carrier present on the membrane and the complex then translocated from one face of the membrane to the other (Table 1.5.1). It is specific, saturable, and competitively blocked or inhibited by antagonists, which utilizes the same carrier. It is again classified into:

a. Active transport: Transport needs energy and movement occurs against the concentration gradient, which is blocked or inhibited by metabolic poison.

The metabolic energy, which is required for active transport, is often generated by the enzyme known as $\text{Na}^+ - \text{K}^+ - \text{ATPase}$. The active transport occurs only in one direction and is saturable (see Fig. 1.5.3).

Example: Hepatic transport of digitalis glycosides, Internal uptake of 5 FU, and Ca^{++} absorption in intestine.

b. Facilitated diffusion: It is just like diffusion (i.e. carrier mediated), but is more rapid and translocation may occurs for non-diffusible substrates. Drug or substrate move along their concentration gradient and therefore no energy is needed or required (Fig. 1.5.3).

It is also specific and saturable.

Example

- Amino acid in brain
- Antiviral drugs
- Adenosine like drugs, etc.

Table 1.5.1: Showing basic modes of drug transport across a membrane

Mechanism	Energy required	Carrier	Direction	Saturable
Passive diffusion	No	No	Down conc. gradient	No
Filtration	No	No	Down pressure gradient	No
Active transport	Yes	Yes	Against conc. gradient	Yes
Facilitate transport	No	Yes	Down gradient	Yes

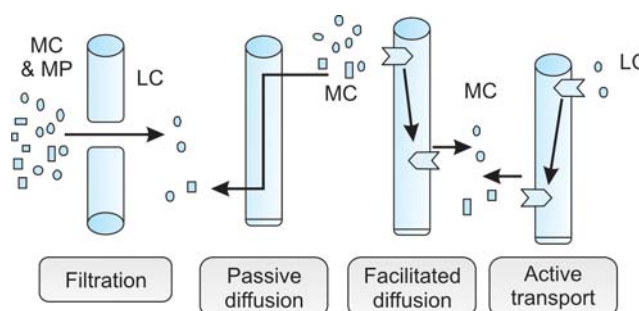


Fig. 1.5.3: Figure showing basic mode of drug transport across a membrane where MC and MP are maximum concentration and maximum pressure while LC means lower concentration

ENDOCYTOSIS

Pinocytosis: *Pino* meaning “I drink”, *cyto* “cell” and *osis* means “process”. It is the process of drinking or engulfing fluid or a drug by the cells in the solution by forming vacuole or vesicles. It is important in transport of big molecules and proteins but not significant in transport of drug.

Phagocytosis: “to eat” It is the process of engulfing particulate matter or substance into the cell. It is also not very significant.

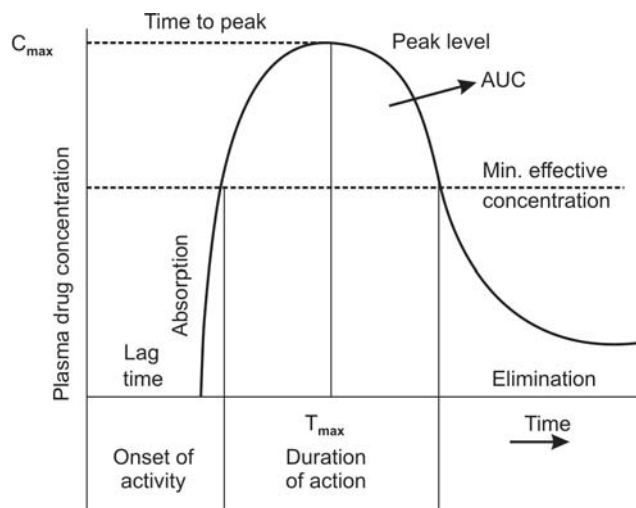
Aspects of Pharmacokinetics which are of daily Clinical Relevance:

- i. Rate and extent of absorption (Bioavailability).
- ii. Volume of distribution (V_d) and distribution pattern.
- iii. Peak and trough plasma concentrations (to be seen in relation to the ‘effective’ and ‘toxic’ concentrations).
- iv. Organs of elimination.
- v. Kinetics of elimination.
- vi. Plasma half-life.

ABSORPTION

Absorption is the movement/transfer of drugs from its site of administration into the blood stream/circulation.

- i. IV administration does not involve absorption, and there is no drug loss (bioavailability is 100%).
- ii. On extra-vascular (non IV) parenteral administration of the drugs, i.e. (PO) per oral, (IM) intramuscular, (SC) subcutaneous and inhalational routes, less than 100% of the administered doses of the drugs may reach the systemic circulation because of **first pass metabolism or effect**.

Factors affecting absorption**A. Pharmaceutical factors and****B. Pharmacological factors.****Fig. 1.5.4:** Plot of plasma concentration versus time

C_{max} : Max. drug level obtained with the dose.

T_{max} : Time at which C_{max} occur.

Lag time: Time from administration to appearance in blood.

Onset of activity: Time from administration to reaching MEC [Min. effect concentration].

PHARMACEUTICAL FACTORS**1. Aqueous solubility**

First step is “Disintegration” of solid dosage forms (i.e. tablets) into fine (small) size particles.

Second step is ‘Dissolution’ which is a rate-limiting step.

Other determinants of the solubility of a drug are:

- Particle size: smaller the size of the particles, faster be the absorption of the drug.
- Salt form and crystalline form
- Water of hydration (hygroscopic property of the drug)
- Nature of adjuvant, i.e. coloring agents, flavoring agents, binding agents, etc.
- Degree of ionization (unionized drugs are better absorbed)

2. Concentration/dosages

- Drug in higher concentration absorbs faster (according to concentration gradient).
- Dosage affect the drugs concentration at its site of action and thus greatly influences the biological response to the drug. The larger the dose, the greater the effect, until the maximal effect is achieved. This is called **dose response relationship** (Fig. 1.5.4).

Pharmacological Factors

- Area of absorbing surface:** If area of absorbing surface is large, absorption is faster. Do you know that the

total surface area of our gut is approximately about half the size of an average football ground.

- Vascularity of the absorbing surface:** Increased blood flow increases absorption of the drug for e.g. increase airflow increases drying of cloths.

3. Routes of administration

- Oral
- Parenteral or
- Topical

ORAL

Effective barrier – Epithelial lining of the GIT.

Factors affecting oral absorption of the drugs

- Lipid: water** partition coefficient : Lipid soluble drugs are absorbed better and faster.
- pH** of the drugs (discussed previously).
- Presence of food:** Food dilute the drugs therefore delay the absorption. Most of the drugs are absorbed better if taken in empty stomach.
- Presence of other drugs/chelating agents:** These substances form chelate with original drug and decreases its absorption from GIT i.e. calcium tablet, tetracycline, etc.
- GIT motility:**

I. Gastric emptying time

On promoting gastric emptying or on decreasing gastric emptying time there occurs:

- Increase in the absorption of the drugs which are unstable at gastric (acidic pH).
- Increase in the absorption of alkaline drugs.
- Decrease in the absorption of acidic drugs.
- Generalized increase in (faster) absorption of drugs by exposing drugs to relatively higher surface area of the intestine.

On retarding gastric emptying or on increasing gastric emptying time there occurs:

- Increase in the absorption of acidic drugs.
- Decrease in the absorption of alkaline drugs.
- Opposite effects of that of above.

II. Intestinal motility

When intestinal motility increases (e.g. diarrhea) there occurs significant reduction in drug absorption.

- GIT disorders:** E.g. certain GIT disorders like achlorhydria, crohns disease, tropical sprue, absence of certain gastric factors decreases absorption of some drugs, etc.

SUBCUTANEOUS/INTRAMUSCULAR

- By this route, the drugs are directly deposited in the vicinity of the capillaries.

- ii. Very large molecules are absorbed through lymphatic.
- iii. Absorption from subcutaneous site is slower than that from intramuscular sites, but both are generally faster and more consistent than oral absorption.
- iv. Large volume of the drug (fluid) can be administered through subcutaneous route (hypodermoclysis).
- v. Application of heat and muscular exercise accelerate drug absorption (by increasing blood flow).
- vi. Application of ice (cold) or administration of SC adrenaline injection along with the original drug, retard the absorption of drug (due to vasoconstriction).

TOPICAL SITES (SKIN, CORNEA MEMBRANE)

Only few (lipid soluble) drugs significantly penetrate intact skin for example nitroglycerine; similarly corticosteroids, organo-phosphorous compounds, tannic acid when applied over skin produce systemic toxicity.

BIOAVAILABILITY

Bioavailability is the measurement of the fraction (F) of the administered dose of a drug that reaches the systemic circulation in unchanged form.

Simply it can be defined as the rate at which and the extent to which the active concentration of the drug is available at the desired site of action (blood stream). It is an absolute term.

- i. Bioavailability of drug injected IV is 100%.
- ii. Bioavailability of orally and rectally administered drug are always less than (<) 100%.
- iii. Bioavailability of IM/SC/ID etc. is < 100%.

Determination of Bioavailability: Bioavailability is determined by comparing:

- i. Plasma levels of a drug after a particular route of administration (i.e. oral route) with,

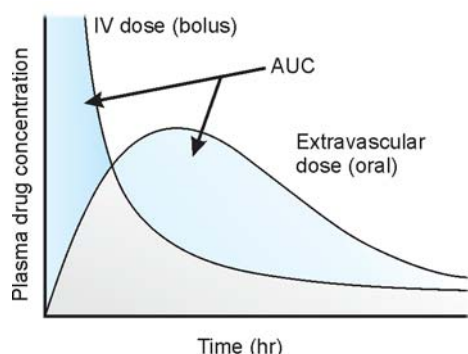


Fig. 1.5.5: Area under curve for an IV bolus and extravascular doses

- ii. Plasma levels of that drug achieved by IV injection. The area under curve [AUC] reflects the extent of absorption of the drug (see Fig. 1.5.5).

Measurement of bioavailability: Comparison of the bioavailability can be done by studying the absorption pattern of two brand products, i.e. brand A and brand B of the same drug. Then the plasma concentration of the drug (in both brands) are plotted against time (hrs.) till plasma concentration has fallen to a predetermined point e.g. 5% of C_{max} (peak value) as shown in Fig. 1.5.6.

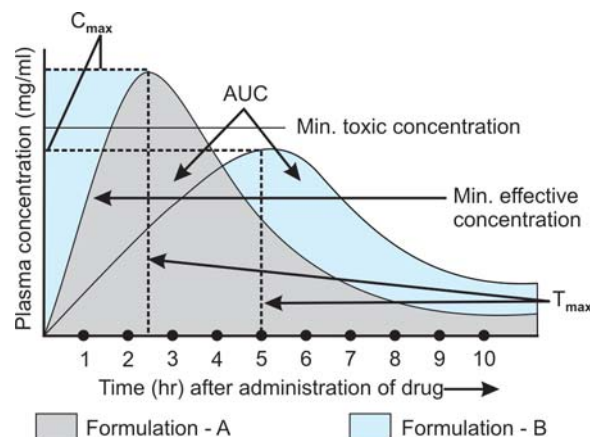


Fig. 1.5.6: AUC of formulations A and B

From this curve, we obtained three important parameters

- I. C_{max} : Peak plasma concentration.
- II. T_{max} : Time to attain C_{max} (peak value).
- III. **AUC**: Area under curve (at 5% of the peak value).

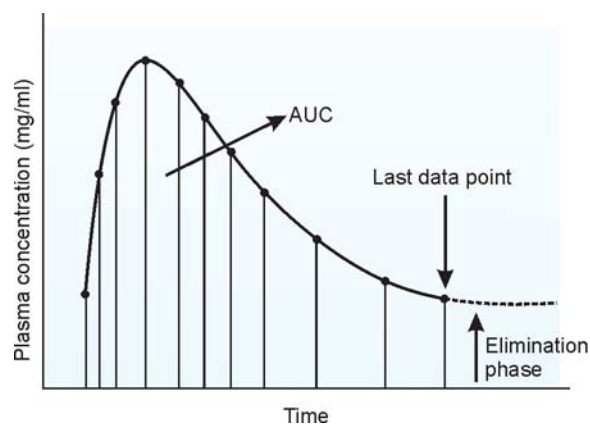


Fig. 1.5.7: AUC (Area under curve)

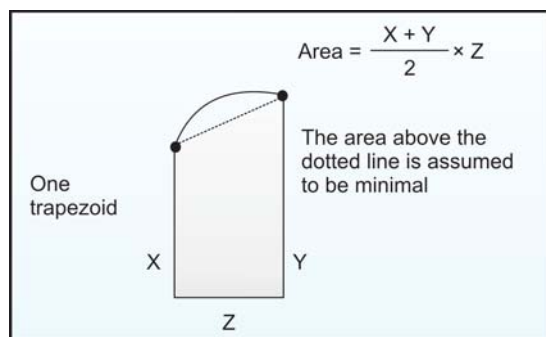


Fig. 1.5.8: Calculation of AUC using trapezoidal rule

- I. The C_{max} and T are simple indicators for the rate of absorption.
- II. While AUC reflects the extent of absorption and is expressed in $[\mu\text{g}\cdot\text{hr}/\text{ml}]$.
- III. The AUC can be calculated by:
 - Using an instrument called “**planimeter**” which mechanically measures the area of plane (Fig. 1.5.7).
 - By “cut and weight method”: in which we cut out the AUC on a rectilinear graph paper and weigh it on analytic balance.
 - By mathematical method: In which we use **trapezoidal rule** (Fig. 1.5.8).

The bioavailability of any oral dosage can be quantitatively evaluated by comparing AUC obtained after (orally administered single dose) of the drug with that of AUC (obtained after IV injection) [100% absorption].

$$\text{Drug bioavailability (\%)} = \frac{\text{AUC (oral)} \diamond 100}{\text{AUC (IV)}}$$

Factors affecting Bioavailability

1. First pass hepatic metabolism.
 2. Solubility of the drug: Very **hydrophilic** as well as very hydrophobic drugs both are poorly absorbed. For a drug to be readily absorbed, it must be largely hydrophobic yet have some solubility in aqueous solutions.
 3. Incomplete absorption.
 4. Instability of some drugs, i.e.
 - i. Penicillin-G
 - Unstable at gastric pH
 - ii. Insulin
 - Destroyed in acidic pH (discussed previously)
 5. Nature of the drug formulation.
- Factor 2, 3 and 4 affect bioavailability indirectly by affecting drug absorption and are discussed previously in detail, here we are discussing factor 1st.

First Pass Effect/Pre-systemic Metabolism/First Pass Metabolism

Definition: It is the metabolism of the drug during its passage from the site of absorption into the circulation. Some drugs are removed from the portal circulation very efficiently by the liver and metabolized so that the **amount reaching the systemic circulation is significantly less than the amount absorbed** (Fig. 1.5.9).

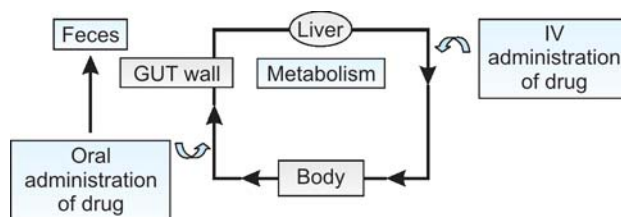


Fig. 1.5.9: First pass metabolism

Few drugs are also metabolized in the walls of intestine, e.g. tyramine, testosterone, nitrites, nitrates lidocaine and pethidine are some drugs, which undergo extensive first pass metabolism (Table 1.5.2).

Routes, which avoid first pass metabolism in liver:

1. Sublingual (isosorbide) and
2. Intravenous: First pass effect bypasses if drug taken; parenterally (xylocaine).
3. Transdermal, intramuscular and subcutaneous routes having bioavailability (< 100 %).

Table 1.5.2: List of the drugs having high first pass effect

Drugs which are not given orally	Drugs which are given orally but in higher doses
Testosterone	Propranolol
Hydrocortisone	Alprenolol
Isoprenaline	Pethidine
Lignocaine	Morphine
	Nitroglycerine
	Verapamile
	Salbutamol

Significance: First pass effect is significant only when inactive metabolites are formed from active ones because there will be no effect (action) of the drug. In reverse case bio-availability as well as toxicity of the drug increases.

BIOEQUIVALENCE: If two or more similar dosage forms of the same drug reach the blood circulation at the same relative rate and to the same relative extent these are called **bioequivalence**.

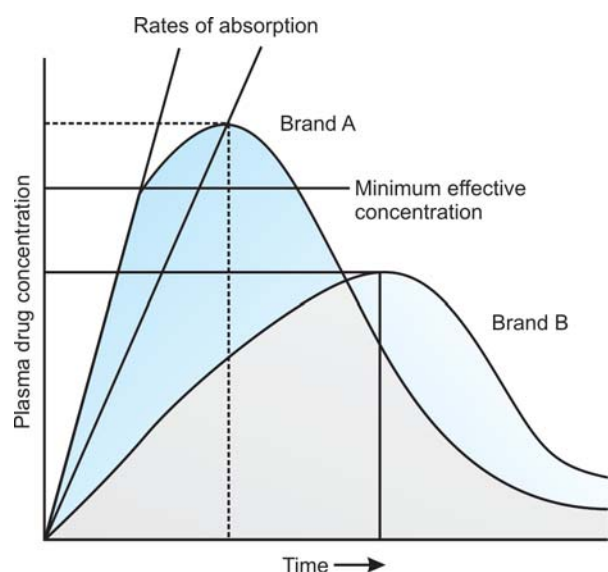


Fig. 1.5.10: The figure shows an example of bioinequivalence. The two formulations differ in rate of absorption. Brand B is more slowly absorbed than Brand A.

Two related drugs are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentration. Two related drugs with a significant difference in bioavailability are said to be **bioinequivalent** (Fig. 1.5.10).

Therapeutic equivalence: Two similar drugs are therapeutically equivalent if they have comparable efficacy and safety.

Drug disposition: The part of pharmacokinetics which deals with distribution, metabolism and excretion of the drug is called as **drug disposition**.

Body compartments: Body can be divided into different (imaginary) compartments, e.g. Intravascular, Extracellular, Intracellular, etc. containing body fluids. Movement (distribution) of drugs into these compartments lead to dilution of the drug. This movement is governed by several factors, e.g. concentration of drug, lipid solubility, etc. Different compartments are shown in Fig. 1.5.11.

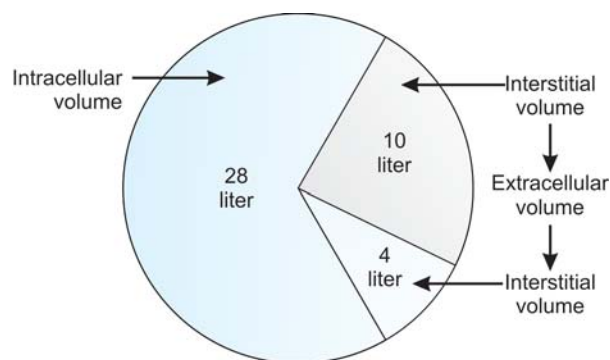


Fig. 1.5.11: Fluid volume within a 70 kg individual

One compartment pharmacokinetics model

This is the simplest and most commonly used Pharmacokinetics model system. This model considers the body as a single homogenous compartment. According to this model, Drug administration occurs instantaneous throughout the body. Clearance (CL) from this compartment occurs in a first order fashion.

$$CL \text{ (Lt/kg min)} = 0.693 \diamond \frac{V_d \text{ (Lt/kg)}}{\text{Plasma } T_{1/2}}$$

In this model, all the tissues and organs to which drug penetrates, behave as single compartment though they were in equilibrium with the blood.

Two compartment model

- This is more common model for distribution and elimination of the drugs because it can describe them better.
- This model is generally used for drugs that are not administered intravenously.
- The distribution rate constant in this model is known as the **alfa half-life, or $t_{1/2\alpha}$** .
- The elimination rate constant in this model is known as the **beta half-life, or $t_{1/2\beta}$** .

Multi-compartment pharmacokinetics model: This considers that different parts of the body such as brain, body fat and muscles, are quite different in terms of their blood supply, partition coefficient for drugs, and the permeability of their capillaries to drug, thus each part of the body can be represented by a separate compartment. This model is used for the drugs that are stored in body depots and for drugs with extensive metabolism or elimination mechanism.

DRUG DISTRIBUTION

Clinical distribution of drugs: Drug distribution is the process by which a drug reversibly leaves the blood stream and enters in the interstitial and/or in the cells (intracellular compartment). A drug must diffuse across cellular membranes if its site of action is intracellular. In this case lipid solubility is important for effective distribution.

1. Importance of blood flow (tissue perfusion rate):

- In most tissues, drugs can leave the circulation readily by diffusing across or between capillary endothelial cells. Thus, the initial rate of distribution of a drug is heavily dependent on blood flow to various organs.
- At equilibrium, or steady state, the amount of drug in an organ is related to the mass of the organ and its properties, as well as to the properties of the specific drug.

2. Capillary permeability

- a. **Capillary structure:** Example: Blood Brain Barrier and Blood CSF Barrier (choroid plexus), they are less permeable because of tightly packed juxtaposed cells. As a rule, only lipid soluble, non ionized form of drugs penetrate more easily to brain as compared to water soluble ionized form of the drugs.

There are five regions in the brain which are relatively permeable and therefore does not constitute part of BBB. These are:

- Pituitary gland
- Choroid plexus
- Pineal body
- Area postrema
- Median eminence.

- b. **Drug structure** (lipid solubility):

Hydrophobic drugs: No net charge therefore diffuse easily.

Hydrophilic drugs: Either positive or negatively charged therefore not diffuses easily.

3. Volume of distribution (V_d): The volume of distribution (V_d) is a hypothetical volume of fluid into which the drug is disseminated. Although the volume of distribution has no physiological or physical basis, it is sometime useful to compare to distribution of a drug with volume of the water compartments in the body.

$$V_d = \frac{\text{Dose administered IV}}{\text{Plasma concentration of drug}}$$

Concentration of drug in

Plasma = **50 mg/L**

$$V_d = 500/50 = 10 \text{ L}$$

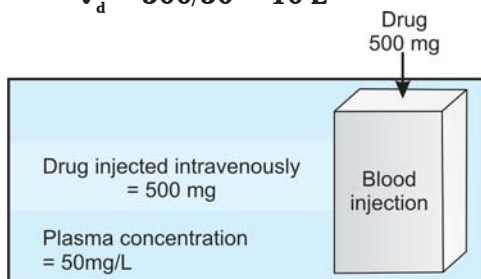


Fig. 1.5.12(a): It is the apparent (not real) volume of fluid in which the drug appears to have been distributed. It is expressed as **L/kg** of body weight.

Apparent volume of distribution: A drug rarely associates exclusively with only one of the water compartment of the body. Instead, the vast majority of the drugs distributes into several compartments, often avidly binding cellular compartments, i.e. lipids (adiposites), proteins or nucleic

acids. Therefore, the volume into which drug distributed is called the apparent volume of distribution or a V_d (Fig. 1.5.12).

Factors governing volume of drug distribution:

- i. Lipid: water partition coefficient of the drug.
- ii. pKa value of the drug.
- iii. Degree of plasma protein binding.
- iv. Affinity for different tissues.
- v. Fat – lean body mass ratio.
- vi. Diseases like CHF, uremia, cirrhosis, etc.

Volume of Distribution can tell us about the pattern of distribution, e.g. (a) if the volume of distribution is equal to plasma volume (3.5 lts in 70 kg adult = 0.05 L/kg), it suggests that the drug remains in the plasma only and is not distributed elsewhere in the body, i.e. it does not leave the vascular compartment (plasma concentration will be high). [e.g. Heparin]

(b) If the volume of distribution is equal to the total body fluids (42 lts, 70 kg = 0.6 lt/kg), it means that the drug is extensively distributed all over the body, including the intracellular compartment (plasma concentration will be low because of dilution). [e.g. Metronidazole, Isoniazid]

(c) If the volume of distribution is more than the total body fluids, it implies that the drug is getting stored somewhere in the body (selective distribution). Plasma concentration will be very low. [e.g. Digitalis, Chloroquine]

(d) Volume of body fluids can increase in diseases like Congestive Cardiac Failure (CCF) or severe anemia while the fluids may be depleted (decreased) in severe dehydration or due to diuretic (drugs that increase urine output) therapy. Volume of distribution and plasma concentration will change when such conditions develop or are corrected.

It also helps to determine loading dose, e.g. Phenytoin.

Clinical significance: In case of poisoning drugs, which increase volume of distribution, are not easily removed by hemodialysis.

Special compartments for drug distribution: Sites of concentration of drug: They can affect the Volume of Distribution

- a. **FAT:** Drug concentrates in fat → lower concentration of drug in the plasma → **high V_d**
- b. **BONE:** Drug concentrates in bone → lower concentration of drug in the plasma → **high V_d**
- c. **TISSUE:** Drug concentrates in tissue → lower concentration of drug in the plasma → **high V_d**
- d. **PLASMA PROTEINS:** Drug binds to plasma protein → higher concentration of drug in the plasma → **low V_d**
- e. **TRANSCELLULAR :** Drug concentrates in non-plasma locations → lower concentration of drug in the plasma → **high V_d**

Enterohepatic circulation: Drugs that are recycled through the enterohepatic circulation will have a lower concentration of drug in the plasma, and therefore a higher V_d .

4. Redistribution: After administration of lipid soluble drug by i.v. route or inhalation, it gets initially distributed to organs with higher blood flow, i.e. brain, heart or kidney, then later on the drug is again distributed to or (taken up by) less vascular but more bulky tissues (muscles and fat). This is called **redistribution**.

Clinical significance: Infrequently, the action of a drug may be terminated by its redistribution from the site of action to other organs. For example, the action of the anesthetic **thiopental** is terminated largely by its redistribution from the brain to more poorly perfused adipose tissue.

5. Barriers to drug distribution:

- **Central Nervous System: Blood Brain Barrier** (discussed previously)
- **Placenta: Placental Barrier** (lipid soluble drugs crosses placenta easily)
- **Testes: Blood Testis Barrier** – Limit the effectiveness of chemotherapeutic agents in treating testicular neoplasms.

Plasma Protein Binding: Although some drugs simply dissolved in plasma water, most of them get bound to plasma and cellular proteins in a reversible manner and in dynamic equilibrium, according to law of mass action.

Free drug + Protein = Drug-Protein Complex

In other words, most drugs having physiochemical affinity for plasma proteins for example (Table 1.5.3):

Important proteins that contribute to plasma proteins:

- Acidic drugs (penicilline) – to albumin
- Basic drugs (quinidine) – to α_1 acid glycoprotein.
- Tissue proteins and nucleoproteins: drugs with $\uparrow V_d$.
- Miscellaneous binding proteins, i.e. transcortin, α_2 globulins, ceruloplasmins, etc.

Clinical significance

- Expressed plasma concentration of the drug refers—bound as well as free drug.
- Increased plasma protein binding; restricts drug to vascular compartment, decreases V_d .
- Bound fraction—not available for action because only free drug diffuses through capillary wall and available for action.
- Increase degree of binding make the drug long acting.
- Drug displacement: one drug bind at various sites on albumin, similarly various drugs bind to the same site.

This can give rise to displacement interaction wherein a drug bound with higher affinity will displace the one having low affinity, e.g. Sulfonamides can displace bilirubin; (kernicterus in neonates) and salicylate displaces methotrexate.

- VI. As a result of plasma protein binding there occurs:
- Decrease in distribution of drug (from plasma to tissue).
 - Decrease in renal excretion (due to reduced filtration).
 - Reduced metabolism.

Table 1.5.3: Examples of plasma protein binding

Acidic drugs to albumin ⁽⁻⁾	Basic drugs to α_1 glycoprotein ⁽⁺⁾ [Orosomucoid]
NSAIDs	Lidocaine
Barbiturates	Quinidine
Penicillin	Beta blockers (propranolol)
Phenytoin	Warfarine
Salicylates	Phenylbutazone

Tissue Storage: Drug stored in various tissues at different concentration, which is specifically based on the specific properties of drug as well as that tissue (Table 1.5.4).

- Active carrier mediated uptake of that particular drug.
- Higher affinity of that particular drug toward a particular tissue.

Table 1.5.4: Examples of tissue storage

Digoxine, emetine	Skeletal muscles
Amphetamine, chlorpromazine	Lungs
Digoxine, emetine, chloroquine	Liver
Cadmium, lead, mercury	Kidney
Iodine	Thyroid
Isoniazide	Brain
Chloroquine	Retina
Tetracycline/heavy metals	Bone/teeth
DDT, ether, diazepam	Adipose tissues

BIOTRANSFORMATION

Other Terms

- Detoxification:** Older term, now discarded.
- Drug-metabolism:** Wider term. It includes catabolism and anabolism. It is the total fate of the drug in the body including absorption, biotransformation and excretion.

Definition of biotransformation: It is a catalytic chemical alteration of nonpolar (lipid soluble) drug or compound

to more polar (lipid insoluble) or to water soluble compound so that they do not reabsorbed in the renal tubule and get easily excreted out through the kidney.

Most hydrophilic (polar) drugs like streptomycin are not biotransformed and are excreted unchanged in the urine.

Important sites for the drug metabolism are:

- Liver: It is the most important, primary and major site of biotransformation for many drugs or xenobiotics.
 - Kidney
 - Intestine
 - Lungs, plasma, placenta, adrenal cortex, skin, etc.
- ⇒ No biotransformation occurs at: dead tissues like nails and hairs.

Biotransformation leads to:

- Inactivation of drug or its metabolites (mostly) example - morphine, phenobarbitone – hydroxybarbiturate, etc.
 - Formation of active metabolite from active drugs
 - Diazepam to desmethyl diazepam
 - Digitoxin to digoxin, etc.
 - Imipramine to desipramine
 - Activation of inactive drug (Such drugs are called pro-drugs)
- Examples:
- Levodopa (inactive) to Dopamine (active)
 - Prednisone (inactive) to Prednisolone (active)

Biotransformation reaction can be classified or occur in two phases

Phase I Metabolism/ Non-synthetic reactions: In phase I reactions, drugs (which are nonpolar) are metabolized (converted) to polar/less-polar metabolites (by introducing new group). In this case the metabolites may be active or inactive. These reactions are mostly microsomal except few (which are non-microsomal). Phase I reaction includes:

- Oxidation
- Reduction
- Hydrolysis
- Cyclization
- De-cyclization

Oxidation

Definition: Loss of electron or addition of O_2 or removal of hydrogen is called oxidation

- Microsomal oxidation:** It requires CYT-P450 enzyme system, CYT-P450 reductase, NADPH (only energy source, no ATP is required) and oxygen, examples are:
 - Aromatic hydroxylation of Propranolol, phenytoin, etc.
 - Aliphatic hydroxylation of Pentobarbital, ibuprofen, etc.
 - Deamination: Amphetamine, etc.
- Non-microsomal oxidation:**
 - Mitochondrial oxidation of Catecholamine.
 - Cytoplasmic oxidation of Alcohol, etc.

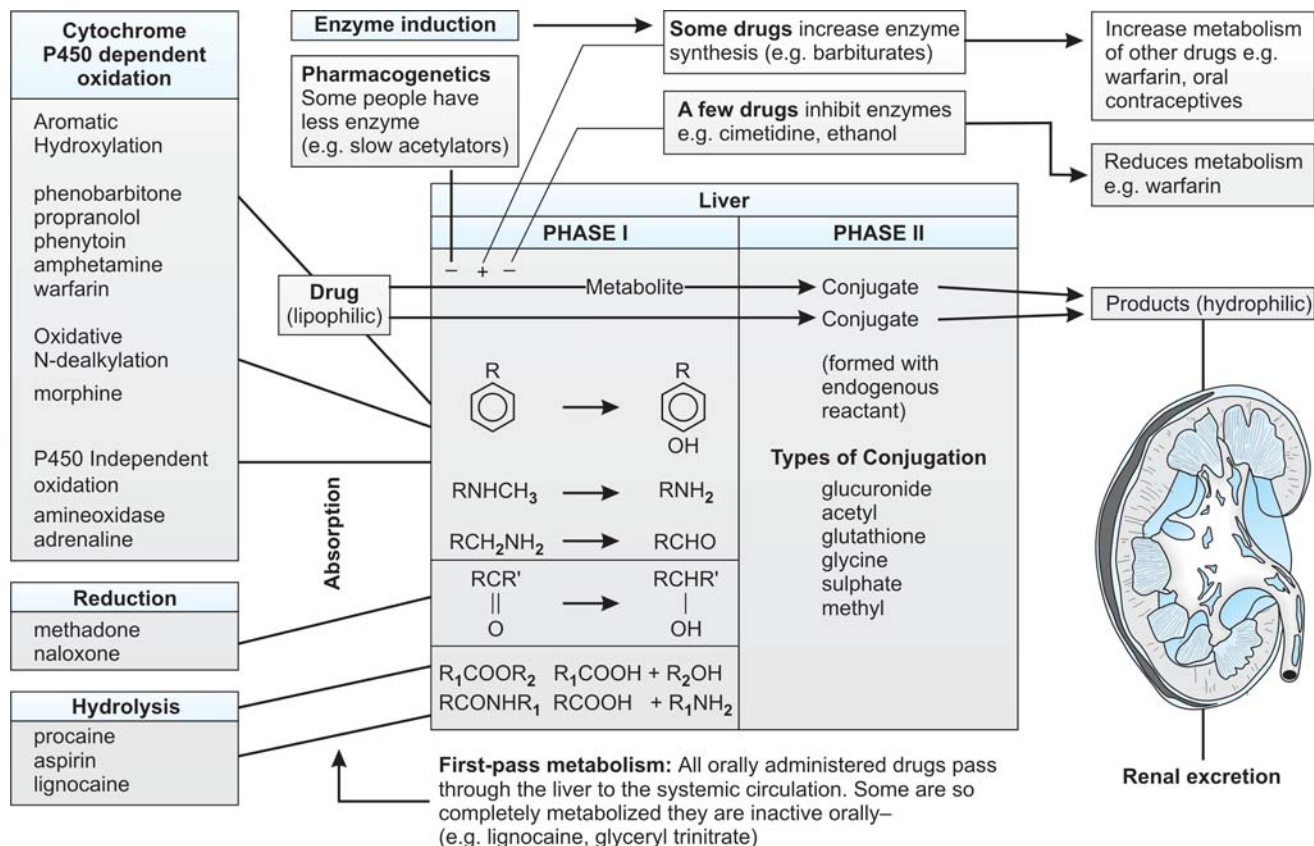


Fig. 1.5.12(b): Showing metabolism of different drugs by different enzymes and their excretion.

Reduction

Definition: Gain of electron or removal of O_2 or addition of hydrogen is called reduction.

a. Microsomal reduction: It requires NADPH, CYT-P450, working in opposite direction, examples are:

- Nitro reduction of Chloramphenicol
- Azo reduction of Prontosil
- Keto reduction of Cortisone

b. Non-microsomal reduction: Hydrolysis: Both microsomal and non-microsomal. It involves addition of water molecule to the drug with subsequent cleavage of drug molecule.

1. Non-microsomal hydrolysis

- Hydrolysis of acetylcholine, succinylcholine and procaine.
- Peptidases (e.g. proinsulin)
- Procinamide and indomethacin.

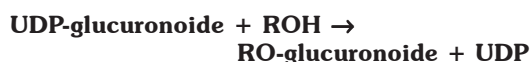
2. Microsomal hydrolysis have also been identified.

Phase II Metabolism/Synthetic/Conjugation reaction: In phase II reaction, the drugs or phase I metabolites that are not sufficiently polar to be excreted rapidly by the kidney are made more hydrophilic by conjugation with endogenous compounds in the liver. Microsomal, mitochondrial or cytoplasmic enzymes mostly catalyze these reactions. The examples includes:

a. Microsomal conjugations:

i. **Glucuronide conjugation.** It is the most common conjugation reaction. It occurs frequently with *phenols, alcohols, carboxylic acids, PCM, morphine, etc.*

- Activated glucuronic acid (UDP – glucuronoide) is formed from glucose-1-phosphate, which then react as follow:



where, ROH is the drug or its metabolites.

- Glucuronoides are generally inactive and are rapidly excreted in urine or bile by anionic transport systems.
- Glucuronoids eliminated in the bile can be hydrolysed by intestinal or bacterial beta glucuronidases, and free drug can be reabsorbed (process is called as **Entero-hepatic Circulation**) and it generally extend the action of drugs.

b. Non-microsomal conjugations:

Acetylation: Slow/fast acetylation, i.e. *isoniazide, sulphonamide, etc.*

Hepatic – N-acetylase displays genetic polymorphism. About 50% of the population acetylate isoniazide (an anti-tubercular drug) rapidly. While the other 50% of

the population acetylates it slowly. Slow acetylation is due to an autosomal recessive gene which is associated with a smaller amount of hepatic – N-acetylase. Slow acetylators are more likely to accumulate the drug and to experience adverse reaction. There is evidence of polymorphism in the acetylation of other drugs, e.g. (hydralazine)

Methylation: *Histamine, noradrenaline.*

Sulphate conjugation: *Phenobarbitone, steroids.*

Glycine conjugation: *Salicylic acid*

Glutathione conjugation: *Ethacrynic acid*

Amino acid conjugation: *PAS, nicotinic acid, etc.*

All the above mentioned reactions carried out by certain enzymes which can be classified as:

Microsomal enzymes: The sub-cellular components of smooth surface endoplasmic reticulum (SER) in liver, lungs and kidney contain membrane associated enzyme, which is responsible for drug oxidation.

The primary component of this enzyme system are: CYT-P450 (heme protein), NADPH, Cyt. C_{Reductase}, (mixed function oxidases), etc.

- These enzyme system has been termed as **mixed-function-oxygenase**.
- These microsomal enzymes are nonspecific in nature.
- They can be induced.
- They can metabolized only lipid soluble drugs.
- CYT-P450 – 2 and CYT-P450 – 3A are responsible for the metabolism of most of the drugs.
- CYT-P450 3A4, metabolizes many drugs in GIT, where it reduces bioavailability of many orally absorbed drugs.

Non-microsomal enzymes: These are present in cytoplasm (cytosole) and mitochondria of hepatic cells and other tissues like plasma. These includes:

- Alcohol dehydrogenase and aldehyde dehydrogenase*, which oxidizes ethanol to acetaldehyde and acetate and required NAD.
- Xanthine oxidase* converts hypoxanthine to xanthine and finally to uric acid.
- Tyrosine hydroxylase:* It is important in synthesis of adrenergic neurotransmitters.
- Monoamine oxidases:* Important in the metabolism of catecholamines and serotonin. Examples: Esterases, amidases, transferases, conjugates, etc.
- Others:* Their specific characteristics are that they are non-inducible.

Clinical significance: *Both enzymes are deficient in the newborn especially in premature babies, making them more susceptible to many drugs.*

Factors affecting drug metabolism

- Genetics: Most important factor is genetically determined polymorphism, e.g. acetylation of isoniazide.
- Chemical properties of the drug: enzymatic induction and enzymatic inhibition.
- Routes of drug administration.
- Diet
- Dose, gender.
- Disease
- Circadian rhythm, etc.

Hofmann Elimination of drug: *It is the inactivation (biotransformation) of drug in the body fluid by spontaneous rearrangement of the molecules without the agency of enzymes, e.g. atracurium*

Enzymatic Induction: Certain drugs for example: *Phenytoin, rifampicin* etc. on repeated administration stimulate or induce the growth of endoplasmic reticulum. This stimulation (induction) increases hepatic microsomal enzyme activity and / or quantity, resulting in increased metabolism of other drugs, metabolized by the same enzymes, when given together. Usually this enzymatic induction is most prominent in liver, can also occur in lungs, placenta and kidney. Alcohol and cigarette smoking both causes autoinduction.

Example: Failure of contraception with OCP when given with phenytoin or rifampicin.

Importance of enzyme induction:

- May lead to drug interaction and may ↑ drug metabolism.
- It can lead to drug toxicity.
- May lead to development of tolerance and failure of drug response, specially on autoinduction.
- Inducers may be used in the treatment of certain diseases, e.g. gilbert diseases, neonatal jaundice, etc.

Inducers of CYT-P450 Complex: Drugs that increase the production of Cytochrome-P450 enzymes.

- Anti-convulsants: **Phenobarbitol, Phenytoin, Carbamazepine** induce **CYT-P450-3A4 enzyme**.
- Phenobarbitol, Phenytoin** also induce **CYT-P450-2B1 enzyme**.
- Polycyclic Aromatics (PAH):** Induce **CYT-P450-1A1 enzyme**.
- Glucocorticoids** induce **CYT-P450-3A4 enzyme**.
- Chronic Alcohol, Isoniazid** induce **CYT-P450-2E1 enzyme**. This is important as this drug activates some carcinogens such as Nitrosamines.
- Chronic alcoholics have up-regulated many of their CYT-P450 enzymes.

Enzymatic Inhibition: Similarly certain drugs for example: *cimetidine, diltiazem*, etc. decreases hepatic microsomal

enzyme activity and/or quantity, resulting in decreased metabolism of other drug metabolized by the same enzyme, when given together.

It is a rapid process and usually reversible but sometime it could also be irreversible.

In such cases kinetics of elimination changes from first order to zero order, which is a dose dependent entity, and can precipitate toxicity of the object drug.

Clinical significance

- Enhance toxicity of the drugs, e.g. Precipitation of cardiac arrhythmias with terfenadine when given with chloramphenicol.
- Severe respiratory depression when morphine given with MAOIs (Mono-amine oxidase inhibitors).
- Increased accessibility of L dopa in brain when given with carbidopa.
- Reversal of skeletal muscle paralysis due to d tubocurarine by neostigmine.

Inhibitors of CYT-P450 complex: Drugs that inhibit the production of Cytochrome-P450 enzymes:

- Acute Alcohol** suppresses many of the CYT-P450 enzymes, explaining some of the drug-interactions of acute alcohol use.
- Erythromycin, Ketanazole** inhibit **CYT-P450-3A4 enzyme**.
- Terfenadine (Seldane)** is metabolized by **CYT-P450-3A4 enzyme**, so the toxic unmetabolized form builds up in the presence of Erythromycin. The unmetabolized form is toxic and causes lethal arrhythmias. This is why Seldane was taken off the market. **Chloramphenicol, Cimetidine, Disulfiram** also inhibit CYT-P450's.

Enterohepatic Circulation: Drugs and their metabolites are secreted into the bile are transported to the intestine and appear again in the blood. This recycling of the drug is called enterohepatic circulation. Examples: *tetracycline, erythromycin, digoxine, morphine, chromoglycate, rifampicin, ampicillin, oral contraceptive pills*, etc.

ELIMINATION [EXCRETION OF THE DRUGS]: Drug excretion is the process by which a drug or its metabolites is eliminated from the body. The kidney is the most important organ for excretion. Other routes includes biliary tract and the feces, lungs (expired air), sweat, saliva, skin, tears, etc.

Renal excretion [Urine]: It is the most important channel of excretion for most of the drugs (Fig. 1.5.13). It includes:

- Glomerular filtration
- Tubular secretion (active carrier mediated), i.e. Penicillin, cephalosporine, etc.
- Tubular reabsorption: pH dependent, i.e. Aspirin.

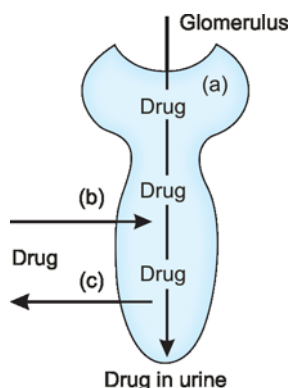


Fig. 1.5.13: Renal excretion of drugs

- a. Glomerular filtration:** Clearance of the apparent volume of distribution by passive filtration. Filtration is a nonsaturable linear function. Ionized and un-ionized forms of drug are filtered but protein-bound drugs molecules are not.

Drug with MW < 5000 -----> it is completely filtered.

Inulin is completely filtered, and its clearance can be measured to estimate Glomerular Filtration Rate (GFR).

$$\text{Rate of elimination} = \text{GFR} + \text{As} - \text{R (active or passive)}$$

Where GFR = Glomerular filtration rate

As = Active secretions and

R = Reabsorption (active or passive)

- b. Tubular secretion:** Active secretion occurs in PCT. Specific compounds that are secreted are:

- i. **Para-Amino Hippurate (PAH)** is completely secreted, so its clearance can be measured to estimate Renal Blood Flow (RBF).

- ii. **Penicillin-G** is excreted by active secretion.

Clinical significance: Probenacid inhibits and blocks the tubular secretion of penicillin and amoxicillin, thereby increasing the plasma half-life and effectiveness of penicillin in the treatment of certain infective diseases.

- iii. **Anionic System:** The anionic secretory system generally secretes weak ACIDS:

- Penicillins, Cephalosporins, Salicylates
- Thiazide diuretics
- Glucuronide conjugates

- iv. **Cationic System:** The cationic secretory system generally secretes bases, or things that are positively charged.

c. Reabsorption

- i. It may occur throughout the tubule. When passive diffusion is employed, only the unionized form of a drug is reabsorbed, depending on its lipid solubility.
- ii. **Ion-Trapping:** Drugs can be “trapped” in the urine, and their rate of elimination can be increased, by adjusting the pH of the urine to accommodate the drug. This is useful to make the body get rid of poisons more quickly.
 - To increase excretion of acidic drugs, make the urine more basic by NaHCO_3^- .
 - To increase excretion of basic drugs, make the urine more acidic by NH_4Cl or vitamin C.

Biliary excretion: Some drugs are actively secreted in the biliary tract and excreted in the feces. Some of the drug may be reabsorbed via the enterohepatic circulation.

Transporters: The liver actively transports generally large compounds (MW > 300), or positive, negative, or neutral charged molecules.

- a. Anionic Transporter:** Transports some acids, such as Bile Acids, Bilirubin Glucuronides, Glucuronide conjugates, Penicillins, etc.

- b. Neutral Transporter:** Transports lipophilic agents, such as:

- Steroids
- Ouabain

- c. Cationic Transporter:** Transports positively charged agents, such as *n*-Methylnicotinamide, tubocurarine.

Charcoal can be given to increase the fecal excretion of these drugs and prevent enterohepatic reabsorption.

Cholestyramine can be given to increase the rate of biliary excretion of some drugs.

Feces: Apart from unabsorbed fraction in GIT (i.e. MgSO_4 , bacitracin, neomycin, etc.) most of the drug present in the feces is derived (excreted) from the bile example: Rifampicine, tetracycline, ampicilline, MgSO_4 , streptomycin etc.

Lungs: (Exhaled air) Gases and volatile liquids like general anesthetics, alcohol, etc. eliminated through exhaled air.

Saliva and sweat: Example: rifampicin heavy metals, metronidazole, theophylline, phenytoin, Li, KI, etc. are secreted through saliva, while urea derivative are secreted through sweat.

Milk: As a rule, basic drugs for example morphine, penicillin, erythromycin, pethidine, OCP, metronidazole, antihistaminic, etc. are excreted more through milk as compared to acidic drugs (Fig. 1.5.14).

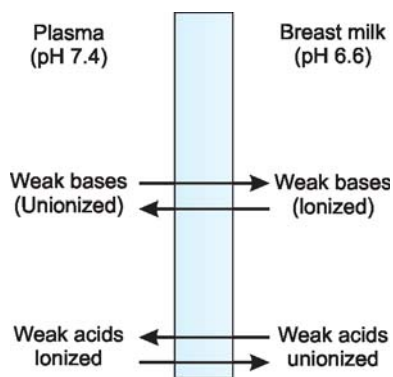


Fig. 1.5.14: Excretion of drugs in milk

Tears: Example: rifampicine and minocycline, etc.

Hair: Example: arsenic, Hg salts and iodides are excreted in hair.

CLINICAL PHARMACOKINETICS

Plasma Concentration: It is the concentration of the drug in the plasma. It is expressed as mg or mcg or Units per ml. It is presumed that the concentration of the drug at the site of action will be proportionate to the plasma concentration (Fig. 1.5.15).

Exceptions

- The drugs which are selectively distributed.
 - Hit and Run drugs.
- Peak Plasma Concentration: **Maximum** plasma concentration achieved after administering a dose of the drug. [C_{max}]

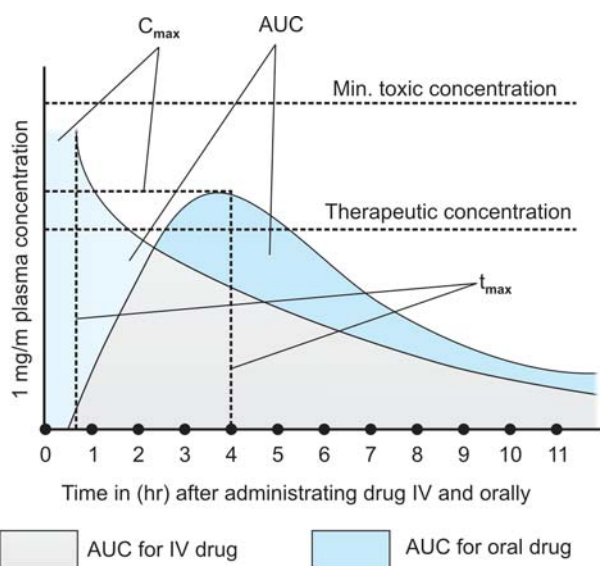


Fig. 1.5.15: Area under curve (AUC) for a drug given parenterally and orally.

- Trough Plasma Concentration: **Minimum** plasma concentration after a dose of the drug (end of the dose).
- Steady State Concentration: **Average** concentration of the drug in the plasma after reaching [C_{ss}] the steady state (usually after 4-5 half lives).

Half-Life Period and Biological Half-Life

Half-life period is the time in which any process is completed by 50% while **biological half-life** is the time in which, any biological process reduced to its half, i.e. by 50%.

Clearance (CL): It is the quantitative measure of the rate of removal of a drug from the body or specific body compartment. It is represented by CL_{total} (total body clearance).

$$CL_{total} = CL_R + CL_{NR(Liver)}$$

Where, CL_R = Renal clearance, while CL_{NR} = Nonrenal clearance (mainly liver and others). Without secretion/re-absorption $CL_R = GFR$.

Total body clearance relates the volume of distribution (V_d) and the first order elimination rate constant (k); $Cl (mL/min) = K (min^{-1}) \times V_d (mL)$.

$$CL = K \times V_d$$

$$K = \frac{0.693}{t_{1/2}}$$

Creatinine Clearance

Definition: It is a measure of glomerular filtration rate (GFR) i.e. the volume of fluid filtered by glomeruli in one minute. About 98-99% of this fluid is reabsorbed but the creatinine once filtered is only slightly reabsorbed therefore:

$$[Creatinine]_{Plasma} \diamond Creatinine\ Clearance = \frac{[Creatinine]_{Urine} \diamond Urine\ flow\ rate}{[Creatinine]_{Urine}}$$

→ but if urine collection is unreliable, use this formula:

$$Creatinine\ Clearance\ (mL/min) = \frac{(140 \diamond Age\ in\ yrs) \diamond (wt.\ in\ kg)}{72 \diamond Serum\ Creatinine\ in\ mg/dL}$$

(for male)

→ For female, multiply above by 0.85.

Plasma Clearance: Amount of plasma that appears to have been cleared of the drug in a given time, i.e. (The apparent volume of blood/plasma from which a drug is cleared per unit of time). It is expressed as **mL/min**. Thus, it is a function of time as well as body mass. Generally,

clearance is interpreted as an indicator of elimination of the drug, however, clearance of plasma can also be due to selective distribution (sequestration / storage) of the drug.

$$CL = \frac{\text{Rate of elimination}}{\text{Plasma concentration}}$$

a. Renal Clearance: It measures the volume of plasma that is cleared of drugs per unit time

$$\text{Renal Clearance} = \frac{U \diamond V}{P}$$

U = Concentration of drug/ml of Urine

V = Volume of urine excreted/minute

P = Drug concentration/ml plasma.

- A drug excreted by filtration alone (e.g. inulin) will have a clearance equal to the GFR (125 mL/min).
- A drug excreted by complete filtration and secretion (e.g. para-aminohippuric acid, **PAHA**) will have a clearance equal to renal plasma clearance (650 ml/min).
- Clearance value between 125 and 650 mL/min suggest a drug is filtered, secreted, and partially reabsorbed.

Clinical Importance

- Renal clearance can be affected by various factors including; age, diseases and other drugs.
- Clearance of a drug reduced significantly in presence of renal failure (chances of toxicity specially with the drugs with lower therapeutic index).
- A reduction in plasma protein may occur in **Glomerulonephritis** which may affect the plasma concentration of the drug.

b. Hepatic Clearance

i. Extraction by the Liver: It is because of the higher blood flow (1 ml/gm/min) to the liver and because of its larger size (approx 1500 g).

ii. The extraction ratio

$$= \frac{\text{amount of the drug removed in the organ (liver)}}{\text{amount of drug entering the organ (liver)}}$$

iii. Extraction ratio (ER) = 1, means drug is completely extracted by the liver and its hepatic clearance $\cong$ 1500 ml/min.

iv. If a drug is taken orally its bioavailability decreases (because of high first pass extraction). A drug, with $ER \cong 0.6$, would have 40% bioavailability.

- v.** In presence of any hepatic disease, drugs with high first pass **extraction (E)** may reach the systemic circulation in higher amount and therefore produces toxicity.

Kinetics of Elimination of Drugs

Elimination of a drug from the body occurs in two ways: First Order Kinetics and Zero Order Kinetics.

First Order Kinetics (Exponential Kinetics): Here the drug is eliminated in a **fixed proportion (%)** of the amount present in the body, in a unit period. The amount excreted therefore will progressively decreases.

Clearance is constant, therefore:

[Plasma concentration $\propto$ R] where R = rate of elimination, i.e. if P_c increases, simultaneously R also increases.

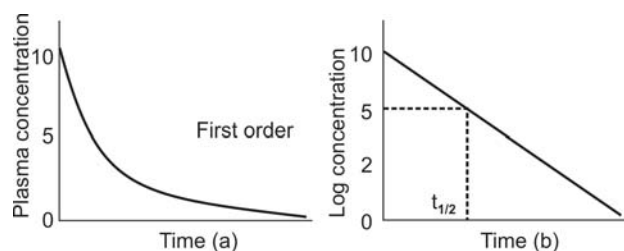


Fig. 1.5.16: Rate of drug elimination and plasma concentration

- A constant fraction of the drug is eliminated at a constant interval of time.
- The rate of drug elimination is directly proportional to its plasma concentration**, i.e. the $t_{1/2}$ of any drug following first order kinetics of elimination would **always remain constant** irrespective of the dose. (Fig. 1.5.16a).
- A plot of the log [conc.] vs- time is linear. (Fig. 1.5.16b).
- After a single dose about 97% of the drug gets eliminated after five [5] half lives ($t_{1/2}$).
- If a fixed dose of the drug is administered at every ($t_{1/2}$), at-least 4 to 5 ($t_{1/2}$) would be needed for achievement of its (C_{ss}), steady state plasma concentration in the body.
- Majority of the drugs obeys first order kinetics of elimination.
- The half life ($t_{1/2}$) of the elimination can be calculated from the formula:

$$(t_{1/2}) = 0.693/K$$

$$\text{Plasma } t_{1/2} = 0.693 \diamond \frac{V_{pt} (\text{Lt/kg})}{CL_{pt} (\text{Lt/kg/min})} \rightarrow V_d \text{ of patient} \rightarrow \text{Clearance in patient}$$

Zero Order Kinetics (Linear Kinetics): In this type of elimination, a **fixed or constant amount** of the drug is eliminated in a given period of time, irrespective of its amount or the concentration present at that time.

- In this case the rate of elimination is independent of the concentration of the drug in the plasma.
- A plot of the drug concentration vs time is linear (Fig. 1.5.17).
- $t_{1/2}$ of the drug following zero order kinetics of the elimination is never constant.
- Hardly few drugs follow zero order kinetics in true sense for example: **ethyl alcohol (C_2H_5OH)**.
- Phenytoin** and **salicylate** also follows zero order kinetics but at higher concentration.

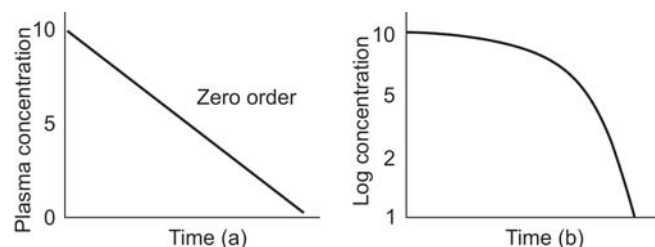


Fig. 1.5.17: Drug concentration vs time

Michaelis-Menten Kinetics or Mixed order kinetics or Saturation kinetics:

In some cases (e.g. Phenytoin, digoxin, warfarine, aspirin, etc.) the drug follows First Order Kinetics when given in smaller doses and changes to Zero Order at higher doses. [First Order at plasma concentration below 10 mcg/ml (approx.) and Zero order at plasma concentration above that].

The clinical uses of such drugs therefore needs proper monitoring and the maintenance of their plasma concentration because in such drugs $t_{1/2}$ changes with the dose of the drug.

Drug Dosage: The **dose** of a drug is the **quantity** needed to be administered to produce adequate concentration in the blood so that the desired response can be obtained in the given patient without development of significant toxicity.

Plasma Half-Life: It is the time, in which the plasma concentration of the drug is reduced by 50% of its original (previous) value. Initially the plasma concentration falls because of the distribution ($t_{1/2}$ **distribution**) of the drug and later, due to elimination ($t_{1/2}$ **elimination**). The **half-life** that we use represents the elimination phase (Fig. 1.5.18). Half-life of some important drugs are discussed in Table 1.5.5.

Time ($t_{1/2}$) and elimination of the drug:

- In $1^{st} \times t_{1/2}$ [50%] of the drug is eliminated.
- In $2^{nd} \times t_{1/2}$ [50 + 25%] = 75% drug is eliminated.
- In $3^{rd} \times t_{1/2}$ [50 + 25 + 12.5%] = 87.5% drug is eliminated.
- In $4^{th} \times t_{1/2}$ [50 + 25 + 12.5 + 6.25%] = 93.75% drug is eliminated.
- In $5^{th} \times t_{1/2}$ [50 + 25 + 12.5 + 6.25 + 3.125%] = 96.88% drug is eliminated.

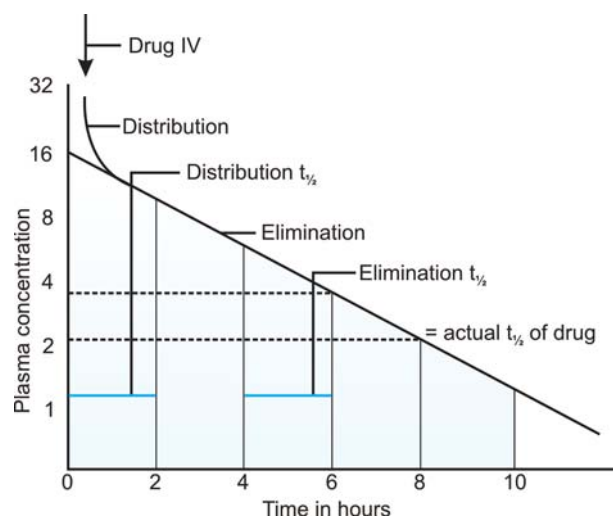


Fig. 1.5.18: Elimination of the drug and plasma half-life

Therefore, in **4-5 half-lives**, approximately complete drug is eliminated.

Table 1.5.5: Half-life of some important drugs

Insulin	5 minutes
Penicillin	30 minutes
Cephalexin	1 hour
Phenobarbitone	120 hours
Diazepam	15 minutes
Phenylbutazone	60 hours
Digitoxin	7 days
Doxycycline	20 hours

Designing a Rational Dosage Regimen

Target Concentration: A rational dosage regimen is based on the assumption that there is a **target concentration** that will remain steady [**Steady State Concentration**] for considerable duration and will produce the desired therapeutic effect without producing toxic effect.

For Drugs with shorter $t_{1/2}$

Repetitive doses

Fluctuations: Drug levels fluctuate as you give each dose. Several factors determine the degree to which drug levels fluctuate.

- There are no fluctuations with continuous IV infusion.
- Slow (more gradual) absorption also reduces fluctuations, making it seem more like it were continuous infusion.
- The more frequent the dosing interval, the less the fluctuations. Theoretically, if you give the drug, say, once every 30 seconds, then it is almost like continuous IV infusion and there are no fluctuations.

Therefore, to obtain **steady state plasma concentration** (Cpss), the drug with shorter half lives ($t_{1/2}$) should be repeated at relatively short intervals, so that they can accumulate in the body until elimination (output) balances input.

$$C_{pss} = \frac{\text{dose rate}}{CL}$$

- From equation it appeared that on doubling the dose rate would double the average Cpss.
- On oral administration of drug, due to first pass metabolism only fraction (f) of the dose in active form reaches the systemic circulation, therefore

$$\text{Dose rate} = \frac{\text{target Cpss} \diamond CL}{f}$$

Steady state concentration and Plateau principle:

When a drug is administered in multiple doses and each dose is given prior to the complete elimination of the previous dose, the mean plasma concentration (C) of the drug during each dose interval rises as shown in the following (Figure 1.5.19):

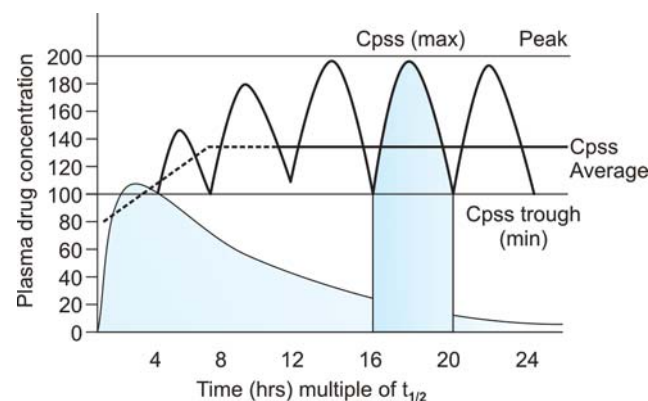


Fig. 1.5.19: Steady state plasma concentration

The plasma concentration will continue to rise until it reaches a **plateau**, or **steady state**. At this time, the plasma concentration will fluctuate between a maximum (**Cpss max**) and a minimum (**Cpss min**) level, but more importantly, **the amount of drug eliminated per dose interval will equal the amount of drug absorbed per dose**.

When a drug is given at a dosing interval equal to its elimination half life, it will reach 50% of its steady state plasma concentration after one half life, 75% after two half lives, 87.5% after three half lives, 93.75% after four half lives, and 96.87% after five half lives. Thus from a practical point of view, regardless of the magnitude of the dose or the half life, the **steady state** will be achieved in **four to five half-lives**.

Although it takes $> 7 t_{1/2}$ to reach mathematical steady state, convention clinical study state is accepted to be reached at 4-5 $t_{1/2}$

1. If a drug is dosed at the same interval as its half-life, then the Cpss will be twice the C_0 (dose) of the drug.
2. If you have a drug of dose 50 mg and a half-life of 12 hrs, and you dose it every 12 hrs, then the steady-state concentration you will achieve with that drug will be 100 mg/L.

$$\text{Clearance at steady state} = \frac{S \diamond F \diamond \text{Dose/T}}{C_{pss \text{ ave}}}$$

Where S = active fraction of the drug; F = fractional absorption; Cpss ave = average plasma concentration at steady state; AUC = Area under (plasma concentration) curve; T = Time (dosing interval)

SOME IMPORTANT ASPECTS

- Dose-amount:** The higher the dose amount, the higher the Cpss.
- Dosage interval:** The shorter the dosage interval, the higher the Cpss
- F: Availability Fraction:** The higher the availability fraction, the higher the Cpss.
- K_{el} : Elimination Constant:** The higher the elimination constant, the lower is the Cpss.
- V_d : Volume of Distribution:** A high volume of distribution means we're putting the drug into a large vessel, which means we should expect a low Cpss.
- Cl: Clearance:** The higher the drug-clearance, the lower the Cpss.

For Drugs with Longer $t_{1/2}$.

- For the drugs having longer $t_{1/2}$ (i.e. digoxin with half life period of 7 days) a dose that is enough to attain the target concentration after single dose, if

administered repeatedly will go on accumulating in the body according to Plateau Principle and then later on it produces severe toxicity.

- ii. Similarly if, dosing will design in such a fashion so as to attain target plasma concentration at steady state, the therapeutic effect will be delayed by about 4-5 half-lives of the drug, i.e. approx 28-35 days for the digitoxin, this may be clinically unacceptable. Therefore such drugs should be administered by initial **loading dose and subsequent maintenance dose**.

Loading dose or priming: The priming dose is that dose which will achieve a therapeutic effect in an individual whose body does not already contain the drug. The effect may be achieved earlier by giving an initial dose that is larger than the maintenance dose. When a drug has a long half-life, this is a way to get to C_{ss} much faster.

1. **Loading Dose = twice the regular dose**, as long as we are giving the drug at the same interval as the half-life.
2. **Loading dose (L_d) = $V_d \times C_{ss}$**
[C_{ss} = plasma concentration at steady state]

Maintenance dose: The maintenance dose is that dose of drug which is to be repeated at regular intervals after the attainment of steady state plasma concentration at target level so as to maintain balance between the input and the output.

Maintenance dose (M_d) = Infusion Rate $\times$ dosing interval,

where, Infusion Rate = $CL \times C_{ss}$

This concept of loading dose and maintenance dose is not restricted for only drugs with longer half-life period. It is also valid for drugs having shorter half-life period and for IV administration in severely ill patients.

Dosing Schedule

1. Drugs with very short $t_{1/2}$ (few minutes only) are usually given by constant i.v. Infusion to maintain their steady state plasma concentration.
2. The drugs with short $t_{1/2}$ (30 minutes to 2 hours) are administered at an interval of 6–8 hours (provided that the drug having a high margin of safety and obeying first order elimination of kinetics).
3. The drugs having $t_{1/2}$ (4 to 12 hours) are usually administered at every $\frac{1}{2}$ life interval (depending upon the drug).
4. The drug having medium $t_{1/2}$ (12 to 24 hours) are usually given at 12 hourly intervals.
5. For the drug having longer $t_{1/2}$ (i.e. digoxin: 40 h, chloroquine: 40 h and diazepam: 40 h); the situation is different. Their V_d is very high and CL is very low therefore

they are cumulative in nature. Since five half-life are needed to reach the steady state concentration. Several days would be wasted in obtaining the desired effect.

- a. *If there is no clinical emergency, i.e. treatment of neurosis or depression with diazepam, there is no problem if steady state reaches after few days, but*
- b. *If there is clinical emergency, i.e. congestive cardiac failure with atrial-fibrillation or hyper-pyrexia due to malaria then such a delay may be fatal for the patient. In such cases, an loading dose that is followed by a maintenance dose is then administered to maintained already attained steady state plasma concentration.*

Therapeutic Drug Monitoring (TDM): It's a fact that patients differ greatly in the amount of drug required to elicit the same response. There are many examples, where the doses of the drugs, that maintain the therapeutic concentration may vary as much as 2 to 10 fold between individuals which might be due to variation in rates of drug metabolism, in distribution and in tissue responsiveness.

Therefore, correlation between plasma concentration and clinical effect is better than that between dose and effect.

What is the theoretical basis for TDM?

Major assumption is that there is a direct and predictable relationship between:

- i. Concentration of drug in plasma.
- ii. Unbound concentration of drug in plasma.
- iii. Tissue concentration of drug (inc. concentration at site(s) of action).
- iv. Pharmacological effect, either efficacy and toxicity.

Situations where therapeutic drug monitoring is useful:

- i. It gives an idea regarding effectiveness of the therapy.
- ii. Specifically to check the failure of response without any apparent reason.
- iii. To reduce the risk of adverse drug reaction, e.g. (otitis media with aminoglycosides), where margin of safety is very less (drugs with low therapeutic index).
- iv. Where, individual variation are very large, e.g. Anti-depressants.
- v. To check patient compliance on a drug regimen: drugs like antiepileptics, antipsychotics; Chlorpromazine, haloperidol, etc.
- vi. To diagnose and treat drug overdoses (poisoning).
- vii. When potentially toxic drugs are used in patients with renal or hepatic failure.
- viii. When there is no quick and reliable assessment of drug effect, e.g. Li for mood disorder.

Situations where therapeutically drug monitoring is of no value:

- Drugs where dose response can be titrated against a quickly and easily measured effect such as Blood pressure (antihypertensives), Body weight (diuretics), Blood sugar (hypoglycemia).
- Plasma concentration has no correlation with effect: **“Hit and run drug”** their effects persist even after the drug has left the plasma, e.g. MAO inhibitors, aspirine, etc.
- In case of prodrug, i.e. where drugs activated in the body.
- Drugs with irreversible action, e.g. organophosphorous poisoning.

Prolongation of “Duration of action of Drug”

Advantages of prolongation of drug action:

- There occurs improvement in patient compliance.
- Prevention of large fluctuation in plasma concentration.
- There occurs reduction in the frequency of administration.
- Overnight maintenance of drug effect without interfering night sleep.

Procedures for prolongation of drug action

A. By interfering (inhibiting) drug absorption.

On oral administration, absorption can be retarded by:

- Reducing solubility of the drug (more polar drugs).
- By administering coated tablets, e.g. slow releasing preparations and (spansules).
- By administering drugs with food.
- By administering drugs with certain other drugs or chelating agent.

On parenteral administration, absorption can be retarded by:

- Reducing vascularity of the absorbing surface or by vasoconstriction.

- Administration of Depot (oily) preparation.
 - Combining drug with protein.
 - Estariification of the drugs.
 - Pellet implantation (hormonal contraceptive methods).
 - Long acting dermal patch.
- B. By inhibiting drug metabolism in the liver.
C. By slowing renal excretion of the drug.
D. By interfering plasma protein binding.

Application of Pharmacokinetic Information: Clinical application of Pharmacokinetics requires having a clear picture in mind about the relationship between Response and Plasma Concentration, and which factors alter the Plasma Concentration (Fig. 1.5.20). When these factors become significant as it occurs in some diseases or with the use of drugs, one has to make adjustments in the dose and frequency of administration, which is called individualization of the dose.

Plasma half-life is affected by distribution (V_d) and clearance (metabolism = liver function and excretion = renal function).

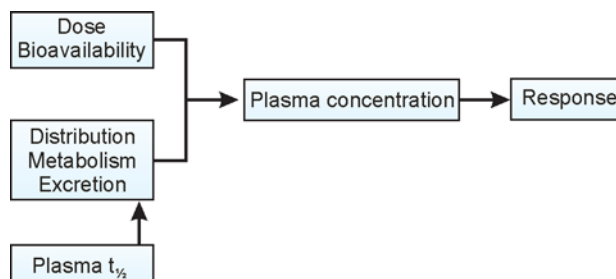


Fig. 1.5.20: Factors that alter the plasma concentration

Pharmacodynamics

DEFINITION

Pharmacodynamics is the branch of Pharmacology (science), which deals with the study of physiological and biochemical effects of drugs and their mechanism of action at macromolecular/sub-cellular/ organ system levels.

Pharmacodynamics is what drug do to the body.

Modes of drug action: It's a fact, that **drugs do not create or impart any new functions to the body, they only modify or alter the existing functions**, which is usually beneficial to the patient. This modification can be brought about by:

Stimulation: It is an increase in the rate of the functional activity of the cell or tissue, e.g. adrenaline stimulates heart (increases H.R.), caffeine stimulate CNS, etc.

Depression: It means reduction in such activity, e.g. acetylcholine depresses heart and decreases heart rate, barbiturate depresses CNS, etc.

Replacement: It can be done for conditions associated with underproduction of endogenous substances, e.g. replacement of a missing or deficient constituent or function, i.e. Insulin in diabetes, dopamine (*levo-dopa*) in parkinsonism, thyroxine in hypothyroidism, etc.

Irritation: It signifies the adverse effects of the drugs on the nutrition, growth and morphology of living tissues. It also produces changes in cellular structure and functions including inflammation, corrosion and necrosis of the cells, e.g. bitterness increases salivary/gastric secretions. Irritant and counter irritant when applied locally also increases blood flow to the supplied organs/tissues.

Cytotoxic effect: Selective toxicity for invading parasites or cancer cells.

a. Antimicrobial action: Selective toxicity for invading microbes and parasites, i.e. Antibiotics, antiviral agents, anti-fungal agents, antiparasitic agents, etc.

- i. Bacteriostatics: they act by inhibiting growth and multiplication of the bacteria.
- ii. Bactericidals: they act by killing bacterial cells.

b. Anticancerous action (chemotherapeutic effect):

Selective toxicity for invading cancer cells.

By modification of the immune status: Vaccines, sera and certain other agents (steroids) act by altering (either increasing or decreasing) the immune status of the body.

Mechanisms

Drugs act:

1. Outside the cell by imparting:

a. Physical actions: A physical property of a drug is responsible for its action.

Physical mass of the drug: Bulk laxative (bran) for treatment of constipation.

Color of the drug: Pleasant colors have (placebo) effects to the patients.

Osmotic activity: MgSO_4 (as a purgative), mannitol (as a diuretic), etc.

Radioactivity: I^{131} (antithyroid drug) act as a weapon for chemical thyroidectomy.

Radio-opacity: BaSO_4 (contrast media for diagnostic purpose) as barium meal.

Smell: Volatile oil (peppermint oil) for soothing effect during cold.

b. Chemical action:

Antacids (aluminium hydroxide) and other salts neutralizing gastric acid.

Chelating agents (BAL, Penicillamine) sequester (chelate) toxic metals.

Oxidizing agent like betadine (povidone iodine) antimicrobial agent.

2. On the cell membrane by:

a. Acting on specific receptor.

Agonists and **antagonists**: Act by binding with specific receptors like adrenaline and propranolol acts on adreno-receptors and acetylcholine and atropine acts on cholino-receptors, etc.

b. Acting on specific ion channel by inducing:

1. Opening of the channels or
2. Closing of the channels, i.e. local anesthetics (Na^+ channel blockers) xylocaine.

c. Inhibition of membrane bound enzyme and pump:

Cardiac glycosides (i.e. digoxin/ digitoxin) inhibit membrane bound Na^+-K^+ ATP_{ase}

d. Imparting physio-chemical interaction (saturation in biophase).

Example : General anesthesia.

3. Within the cell by interfering various metabolic process.

a. Enzymatic induction (stimulation):

Example : Adrenaline stimulates adenylyl cyclase.

b. Enzymatic inhibition.

Example : Phenol / aldehyde [Inhibit enzymes non specifically]. Physostegmine and neostegmine compete with acetylcholine for cholinesterase. (Discussed later.)

c. Inhibition of the transport processes.

Example : Probenacid blocks secretion of penicillin in renal tubules and increases its toxicity.

d. Incorporation into larger molecules/nucleus.

Examples : Sulfa drugs resemble PABA and therefore incorporated in the synthetic process of folic acid in place of PABA.

5 FU incorporate into m-RNA in place of urecil

e. By altering metabolic processes.

Example : Beta lactam antibiotics act by inhibiting cell wall synthesis in bacteria, Sulphonamide acts by inhibiting folic acid synthesis in bacteria, etc.

Targets for drug action: Various targets are therefor the action of drugs on mammalian cells. They can be broadly divided into:

Receptors: They are the specific drug binding sites in a cell or on its surface, which mediate the action of the drug. They are macromolecular proteinous particles. They are located on the membrane (*membrane-receptors*), in the cytosole (*cytoreceptors*), and in the nucleus (*nucleo-receptors*). See Figure 1.6.1.

Ion Channels: Ion channels are of two types:

a. Ligand gated ion channels or channel linked receptors:

These channels are directly linked to a receptor and open only when the receptor is occupied by an agonist. It will be discussed later on in detail.

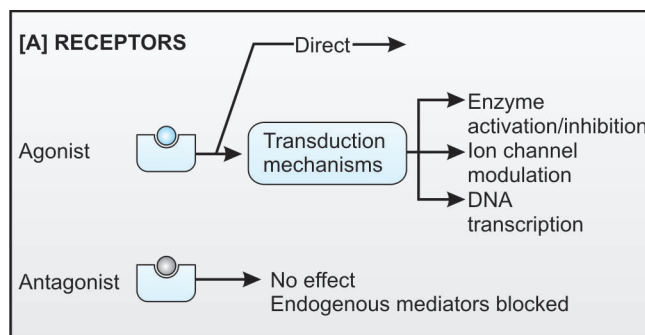


Fig. 1.6.1: Receptors

b. Non-Ligand gated ion channels:

In this types of channels, drug itself bind to the channel protein and alter its functions. Channel functions can also be modified by drugs which bind to accessory sites on the channel protein, e.g. dihydropyridine (which acts on calcium channels and produces vasodilatation) (Fig. 1.6.2).

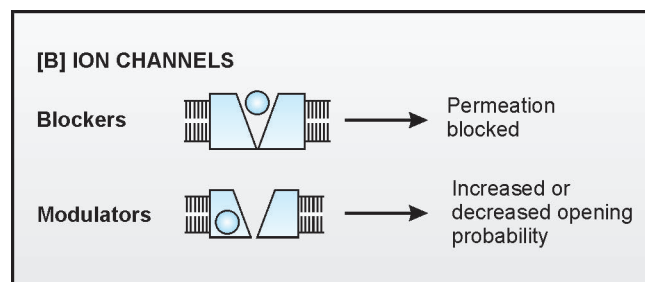


Fig. 1.6.2: Ion channels

Enzymes: Enzymes play an important role in regulating a number of body functions like; synthesis of various metabolites required for cell growth, synthesis of secondary messengers like cyclic AMP and GMP, transport of ions, synthesis and hydrolysis of various neurotransmitters, etc. see Figure 1.6.3.

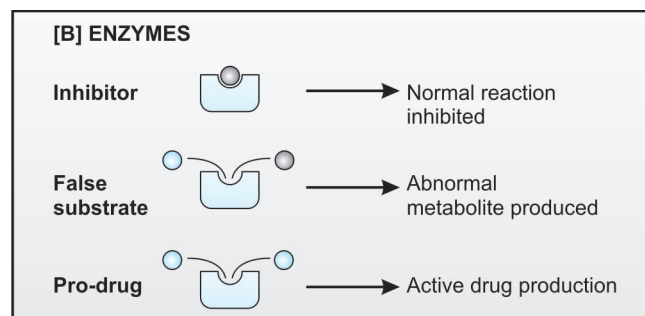


Fig. 1.6.3: Enzymes

Table 1.6.1: Enzymatic inhibition

Competitive inhibition		Non-competitive inhibition
Equilibrium type	Non-equilibrium type	
1. Drug compete with the normal substrate or coenzyme.	Drug bind with same catalytic site of the enzyme but with strong covalent bond therefore substrate is not able to displace it.	Drug bind at the adjacent site of the enzyme, not at the catalytic site and alter the enzyme in such a way that it loses its catalytic property.
2. km increase but Vmax remain unchanged.	km increased but Vmax decreased.	km remain unchanged but Vmax is reduced.
3. Higher concentration of substrate is required to achieve $\frac{1}{2} V_{max}$.	e.g. Methotrexate compete with DHFA for dihydrofolate reductase.	e.g. Digoxin inhibits $Na^+K^+ATPase$. Aspirin inhibit cyclooxygenase.
4. e.g. Physostegmine and Neostegmine compete with Ach for cholinesterase.		

Therefore, enzymes are the important target for many drugs. On binding with enzymes, drugs can either decrease or increase the rate of enzymatically mediated reaction.

1. Enzymatic Inhibition

Many drugs inhibit the action of membrane bound or intracellular proteins. It can be classified as:

- Enzymatic non-specific inhibition. Certain drugs, on coming in contact with enzymes, denatured its protein and thus inhibit the enzyme, e.g. heavy metals like Hg, strong acids, altered phenol, etc.
- Enzymatic specific inhibition. It includes **competitive and non competitive enzymatic inhibition**: see Table 1.6.1.

2. Enzymatic Stimulation: Enzyme stimulation may leads to increase in its (enzymatic) affinity for the substrate so that the **km** (rate constant) of the reaction decreases. It is different from **enzymatic induction** where apparent increase in enzymatic activity can appear, but **km** of the reaction remain constant.

Carrier Molecules (Transporters): The permeation (transport) of the small organic molecules or ions which are lipophobic (less lipid soluble) or more polar, through cell membrane usually requires a carrier protein. The process is energy dependent. There are many examples of such type

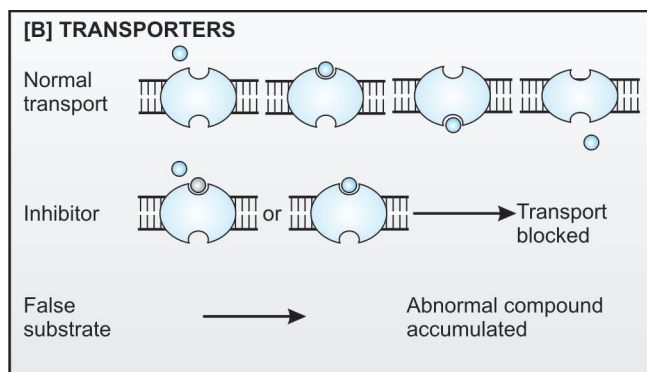


Fig. 1.6.4: Transporters

of transport, i.e. transport of glucose, amino acid into the cells, Na^+ , Ca^{++} ions out of the cells and uptake of neurotransmitter precursors (i.e., choline, tyramine, etc.) by nerve terminal (Fig. 1.6.4).

- This is an important site, where drug can act and block the carrier mediated transport of specific protein and ultimately induces or inhibits any specific function or activity of the cell.

Various types of protein targets for “specific classes drugs” are also known, which are beyond the level of this book.

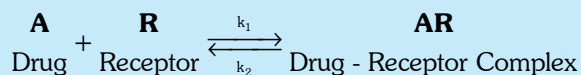
RECEPTORS

History

- Side chain theory:** Proposed by **Paul Ehrlich** (1845 - 1915). He explained that living tissues are composed of large protoplasmic molecules that possess “side chain” and developed this “Side chain theory”. According to him “Corpora non agent nisi fixata” means **a drug will not work unless it is bound**.
- J.N. Langley** (1852-1925) in 1905 proposed that drugs might act upon special sites or receptive substances.

Evidence for action of drugs through receptors:

- Many drugs exhibit SAR (Structural Activity Relationship) i.e. specific chemical configuration is associated with a particular action.
 - Competitive antagonism is also seen between specific agonists and specific antagonists.
 - Just by occupying $1/6000$ th of the cardiac cell surface, Adrenaline / Acetyl-choline produces their maximum effect (Clark).
- 3. Clark (1937)** proposed “**Receptor occupation theory**” based on occupation of receptors by specific drugs. According to him, binding of drugs to receptors necessarily obeys the law of **Mass – Action**.



4. **Ariens and Stephenson** in 1950 introduced the new concepts regarding affinity, efficacy (intrinsic activity) and about spare receptors:

- J.H/Gaddum and HO Schild** also contributed in development of dose-response relationship concept.
- Higher the affinity of the drug for the receptor, lower will be the concentration at which it produces a given level of occupancy.
- The same principles apply when two or more drugs compete for the same receptors; each has the effect of reducing the apparent affinity for the other.

5. **Two state receptor model:** According to this model, receptors are present in two interchangeable states R_A and R_B , which are in dynamic equilibrium with each other.

- The agonist binds specifically to R_A receptors (active) and elicit response. Moreover binding of agonist to R_A leads to conversion of R_B to R_A receptors and therefore, more R_A is available for binding to agonist [full response].
- The antagonist binds preferentially to R_B receptors (inert) and does not elicit any response. Conversely, binding of antagonist to R_B shift the equilibrium in the opposite direction, i.e. R_A to R_B and therefore fewer R_A sites are available to the agonist and therefore higher amount (C) of agonist is required to achieve same level of agonist – R_A complex, i.e. response.
- Partial agonist binds with both R_A and R_B receptors and therefore it elicit only sub maximal levels of R_A binding and response.
- In presence of full agonist, partial agonist compete with full agonist for binding to R_A receptor site.

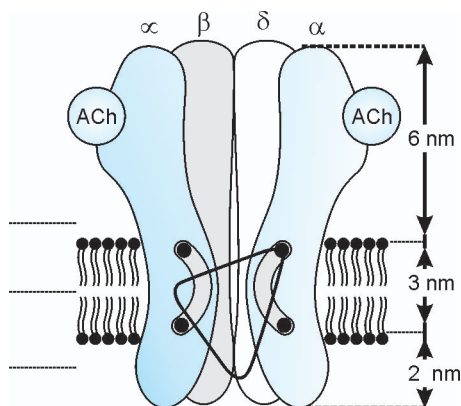


Fig. 1.6.5: Longitudinal section of ACh receptor

Receptor (Definition): Mostly they are macromolecular proteinous particle, which provide binding site, with functional correlates for the drug. Receptors are situated on the surface or inside the effector cells and on combining with

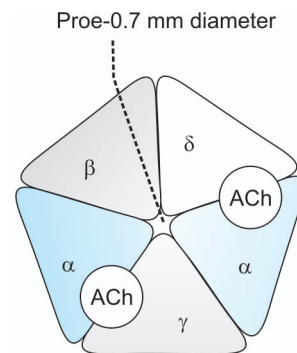
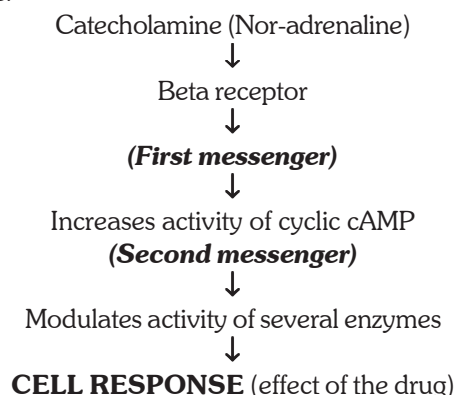


Fig. 1.6.6: Horizontal section of ACh receptor

specific agonist they initiate the characteristic response by undergoing an alteration in its conformation (Fig. 1.6.5 and 1.6.6).

Example:



Functions of the receptors

- Recognition of specific legend molecule, i.e. whether it is agonist or antagonist, etc.
- Transduction of signals, i.e.
 - Propagation of signals from outside to inside of the effectors cells and
 - Amplification of the signals.
- Integration of various regulatory signals, i.e. extracellular and intracellular.
- Maintenance of homeostasis by adopting process of receptor regulation, i.e. up regulation and down regulation.

Physiological receptors: These are the sites where truly physiological transmitters, i.e. autacoids, hormones or any other endogenous mediator bind and elicits physiological response, e.g. *Nor-adrenaline increases heart rate by acting on beta receptor of the heart.*

Drug receptor: As compared to physiological receptor, these are sites where pure exogenous chemicals (drugs) bind and elicit pharmacological response, e.g. *Thiazide receptors, benzodiazepine receptors, etc.*

Silent receptors: These are the inert sites, where drugs bind only as an inert legend without eliciting any pharmacological responses. Actually they are the sites of loss of drug, e.g. *plasma protein*.

Receptor Regulation

Down-regulation: Continuous and prolong exposure of the agonist to tissue leads to, decrease in the number of receptors, this is called **down regulation**, e.g. tachyphylaxis (loss of efficacy with frequently repeated doses) as in asthmatics who uses salbutamol [α_2 – agonist] chronologically on long-term basis.

Up-regulation: When tissues are continuously or prolong exposed to an antagonist, leads to formation of new receptors (increase in the number of receptors), this is called **up-regulation**, e.g. precipitation of angina attack on sudden withdrawal of β -blockers (secondary prophylactic agents).

Important Terminology

- i. **Affinity:** It is the ability of the drug to combine with the receptor.
- ii. **Intrinsic activity:** (Efficacy). It is the ability of the drug to bind with the receptor and induce response. It includes both [Affinity + Response].
- iii. **Agonist:** They are the substances, having both, affinity and max. Intrinsic activity (I max) i.e. they bind with the receptor and produces responses in positive direction.
- iv. **Partial agonist:** They are the substance, which (bind) activate the receptor and produce sub maximal effect, but antagonize the action of full agonist.
- v. **Inverse agonist:** They are the substances, which activate the receptor and produces effect in the opposite direction to that of agonist. (– I max)
- vi. **Antagonist:** Antagonists are the substances, which bind with the receptor, (i.e. they have affinity) occupied them but did not produce any response (0 intrinsic activity). Therefore, they also prevent the action of agonist and partial agonist on the receptors or the subsequent response.
- vii. **Agonist-antagonist:** They are the substances, which act as an agonist at one site (receptor) while act as an antagonist on other site (other receptor).

Receptor Mediated Action: Many drugs produce action by combining with '**Receptor**'. This requires: ability to bind with the receptor (**affinity**) and ability to generate a response (**intrinsic activity**). A drug (or an endogenous substance) acts through its 'own' receptor(s), i.e. combining with certain 'receptor(s)' only. This makes receptor-mediated action highly **specific**.

Since receptors are extremely small (macromolecular components of cells), they cannot be 'seen'. Then how do we know that a particular drug (or endogenous substance) acts through a particular receptor? One way of knowing this is to use **specific antagonists**.

More than one agent may produce similar response (e.g. contraction) in a tissue. The response may be similar qualitatively, but different quantitatively. This indicates their different intrinsic activity, or they may be acting through different receptors.

Drug action: Binding of the drug to its specific receptor is called "**Drug action**". This binding of the drug to receptor can lead to either:

- a. Conformational change in the receptor (in case of agonist) or
- b. Prevention of conformational change on adding agonist (in case of antagonist).

Drug effect: The ultimate effect brought about as a consequence of drug action (binding of drug to receptor) through a series of intermediate steps, i.e. transducer mechanism is called as "**Drug effect**."

Structural Activity Relationship (SAR): There is firm relation between the chemical structure of a drug and its activity. Both the **affinity** of a drug for its receptor and its **intrinsic activity** are determined by its chemical structure. Any minor modifications in the drug molecule may result in major changes in pharmacological properties of the drug. Therefore, information regarding chemical structure is very important and useful especially for:

- a. Synthesis of New drugs with more **specific action** and **lesser adverse (toxic) effect**:
 1. To get more potent drug or to increase or decrease the duration of action of original drug.
 2. To allow (confined) the action of the drug to a specific system (enhanced selectivity among different cells or tissues of the body only).
 3. To control (decrease) the adverse drug reactions, toxicity and other disadvantages associated with the available drugs or to develop a congener (same molecule with altered chemical structure and functions) with a more favorable ratio of therapeutic to toxic effects, or more acceptable secondary characteristics than those of the parent drug.
- b. Development of therapeutically useful competitive (reversible) antagonists of hormones, neurotransmitters and various drugs from their physiological agonist by chemical modification of their structure.
- c. Development of the newer compound (drugs) with favorable pharmacokinetic properties by minor modifications of their original structure.
- d. For understanding about the mechanism of action of drugs.

Recent advances using the structures of receptors and of drug-receptor complexes, determined at atomic resolution by X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy, are even more helpful in the initial design of ligands.

Dose Response Relationship

It has two components:

- Dose – plasma concentration relationship and**
- Plasma concentration response relationship:** When a drug is administered systemically, generally, the intensity of response increases with gradual increase in the dose.

Dose Response Curve: It is the curve obtained by plotting; log doses on x-axis and its consequential responses plotting on y-axis. The curve become sigmoid, and a linear relationship between log of dose and the response are seen in the intermediate (30–70% response) zone.

Basically two types of dose-response relationship have been observed:

a. Quantitative or Graded dose – response relationship:

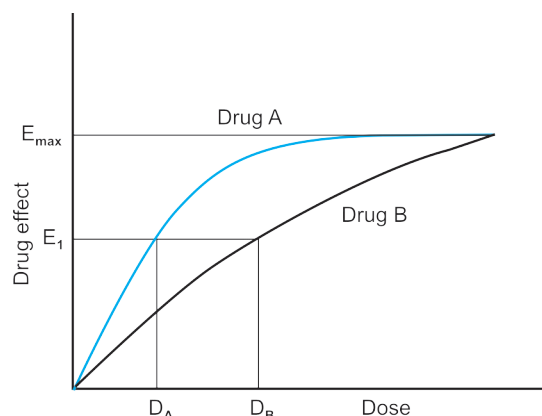


Fig. 1.6.7(a): Graded dose response curves for two drugs A and B

- In this type of relationship entire dose response curve is determined by using a single animal.
- Above threshold dose, as the dose administered to a single discrete organ/tissue increased the pharmacological response also increases in **graded fashion**. The dose response curve is usually a “**rectangular hyperbola as shown in above Figure 1.6.7(a)**”, but plotting the graph-taking logarithm of the dose has a **sigmoid shape**. This log-dose curve is extremely helpful in comparing the various biological activities of various compounds in bioassay.

b. All or none/Quantal dose response relationship:

- In this type of relationship, entire dose-response curve is determined by using groups of animals.
- As compared to graded responses, the quantal responses are all or none. The animals or patients in different groups exposed to different doses and each animal or patient is categorized as responding or non-responding to that particular dose.

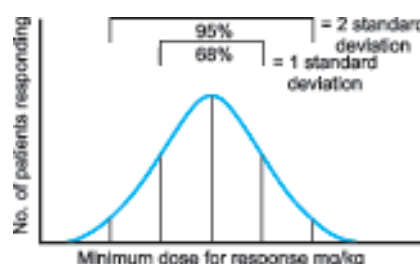


Fig. 1.6.7(b): Frequency distribution curve

- Thus for a given dose: if log dose is plotted on the x-axis, and percentile response on y-axis, a Gaussian (normal) distribution is obtained (Fig. 1.6.7b).

Structural and Signal Transducer Mechanisms: It is the mechanisms of translation of receptor activation (drug action) into functional response (drug effect). In other words it is a complex, multi-step process of amplification and integration of signals. These can be subdivided into four major categories that are mention below.

Receptor families: According to type of molecular structure and the nature of transducer mechanism, there are four receptor “**super-families**” which shares some common architecture:

Type I	: Channel linked receptors
Type II	: G-protein coupled receptors
Type III	: Kinase linked receptors
Type IV	: Receptors which regulate gene transcription.

Out of these superfamilies, first three are transmembrane receptors while the fourth one is intracellular in nature.

Type I: Channel Linked Receptors

Structure

- They are also called **ionotropic** receptors.
- They are membrane receptors, which are directly coupled (or incorporated) with selective ion channels like (Na^+ , K^+ , Ca^{++} , or Cl^-).
- These channels are oligomeric proteins contain approximately twenty transmembrane segments which are arranged in a circle around central aqueous channels (Figs 1.6.8 and 1.6.9).

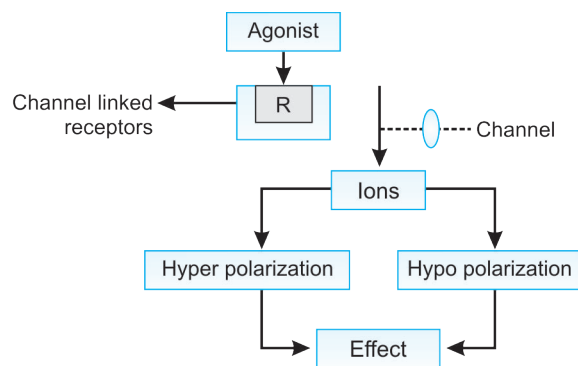


Fig. 1.6.8: Channel linked receptor and its mechanism of action.

Functions

1. They are primarily involved in fast neuro-transmission only.
2. The complete procedure, e.g. ligand binding and opening of the channel takes only **milliseconds**.
3. The subsequent flow of ions through these channels can elicit cellular response in the form of hyperpolarization or depolarization of the cell membrane.

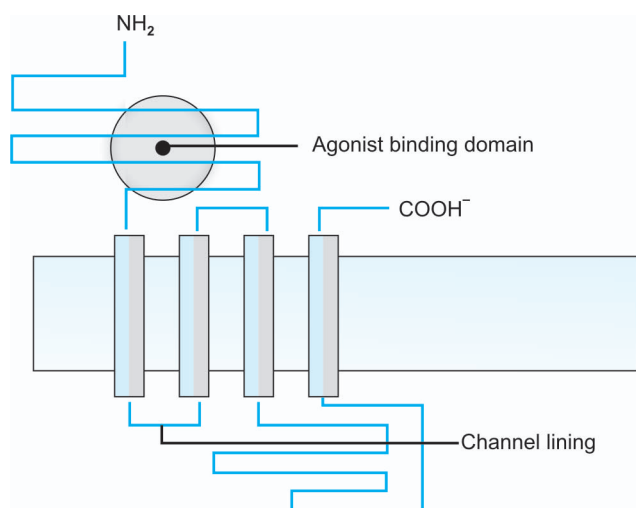


Fig. 1.6.9: Channel linked receptor

Examples:

1. Nicotonic acetyl choline receptor
2. 5-HT₃ (serotonergic) receptors
3. Gabaergic receptors
4. Glutamate receptors, etc.

Type II: G-protein coupled receptors

Structure: They are also known as metabotropic receptor or 7 – transmembrane spanning receptor (because all comprise 7 – membrane spanning segments) (Fig. 1.6.10).

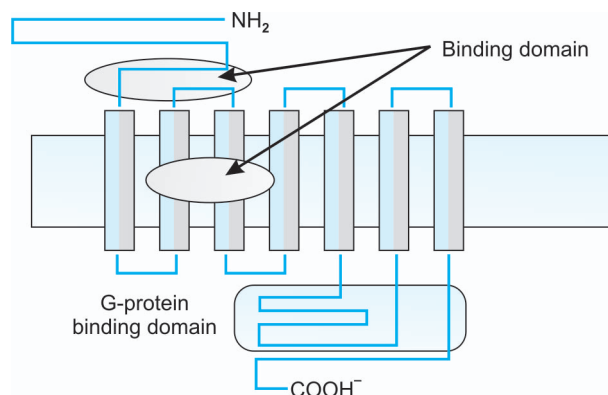


Fig. 1.6.10: G-protein coupled receptor

1. They are membrane receptors. In this type of receptor family, one of the intracellular loop is larger than the other and is linked (coupled) to the intracellular effector system through one or more G-proteins [GTP activated proteins for production of response].
2. The molecules has 7 cylinders, e.g. membrane spanning α -helical segments of hydrophobic amino acid. The intervening segments connect these seven cylinders to form 3 loop on each side of the membrane (i.e. 3 extra-cellular and 3 intracellular loops).
3. The amine (NH₂) terminus probably represent the agonistic binding site is located on the extracellular face, while the carboxy (COOH) terminus represents the binding site for G-coupled protein and is located on the cytosolic side intracellularly.
4. The G-proteins are floating in the membrane and is composed of three subunits (α , β and γ), the α subunit possessing GTP_{ase} activity (Fig. 1.6.11).

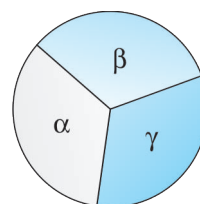


Fig. 1.6.11: Subunits of G-protein

5. Activation of the receptor results into displacement of GDP by GTP. The active α -subunit carrying GTP, dissociates from the other two subunits (β and γ) and either activate or inhibit the effector system.
6. Activation of the effector is terminated when the bound GTP molecule is hydrolyzed, which allows the α -subunit to recombined with other two subunits (β and γ).
7. There are several type of G-proteins which control different effectors by interacting with different receptors few important one are:

8. Specific G-receptors

Gs	Stimulates adenylate cyclase (cAMP)	Open Ca^{++} channels
Gi	Inhibits (decrease) adenylate cyclase (cAMP)	α_2 -Receptors have Gi $\rightarrow$ inhibit post-synaptic adrenergic neurons
Gq	Stimulates Phospholipase-C (IP_3/DAG)	α_1 -Receptors have Gq $\rightarrow \text{Ca}^{+2}$ in smooth muscles
Go	Inhibits Ca^{+2} channels	
Gi	Opens K^+ channels	

Targets for G-protein

- The adenylate cyclase/cAMP system
- The phospholipase – C/inocital phosphate (IP_3 -DAG) and
- The regulation of ion channels.

The Adenyl cyclase/cAMP system

- Activation or stimulation of adenyl cyclase (mediated by Gs protein) results in formation of the intracellular messenger cAMP (See Fig. 1.6.12).
- cAMP activates various protein kinases which control cell functions in different ways by causing phosphorylation of various enzymes, for example, in heart muscles cAMP activates protein kinase [pKa] which directly or indirectly increase Ca^{++} entry into the cells, thereby increasing the force of contraction of heart muscles e.g. β -receptor in the heart muscles.
- Similarly Gi inhibit adenyl cyclase and thus reduces cAMP production thereby inhibiting further cascade

results into relaxation (e.g. M_2 receptors) in heart muscles. Lipolysis and hormone synthesis also take place in similar fashion (Fig. 1.6.12).

- Xanthines: Caffeine** inhibits phosphodiesterase $\rightarrow$ cAMP.
- Desensitization**
 - beta-Arrestin Kinase (beta ARK)** is activated by tonically high cAMP levels. cAMP phosphorylates beta ARK to activate it.
 - beta ARK phosphorylates the regulatory domain of the target receptors $\rightarrow$ prevent cAMP activation.

The Phospholipase – C/Inocital phosphate (IP_3 -DAG) System:

- Stimulation of phospholipase C (mediated by Gq protein) results in formation of the intracellular messengers IP_3 (inositol 1,4,5- triphosphate) and DAG (diacylglycerol) from the membrane phospholipid PIP_2 (phospholipid-phosphatidyl- inositol, 4, 5-biphosphate).
- IP_3 acts to increase free cytosolic Ca^{++} by releasing Ca^{++} from intracellular compartments like (T. tubules). This increases “free Ca^{++} ” initiates many actions which includes:
 - Contraction
 - Secretion
 - Hypopolarization of the membrane and
 - Enzymatic activation.
- While, DAG act by activating protein kinase (Pkc) which ultimately controls many cellular functions by phosphorylating various proteins (Fig. 1.6.13).

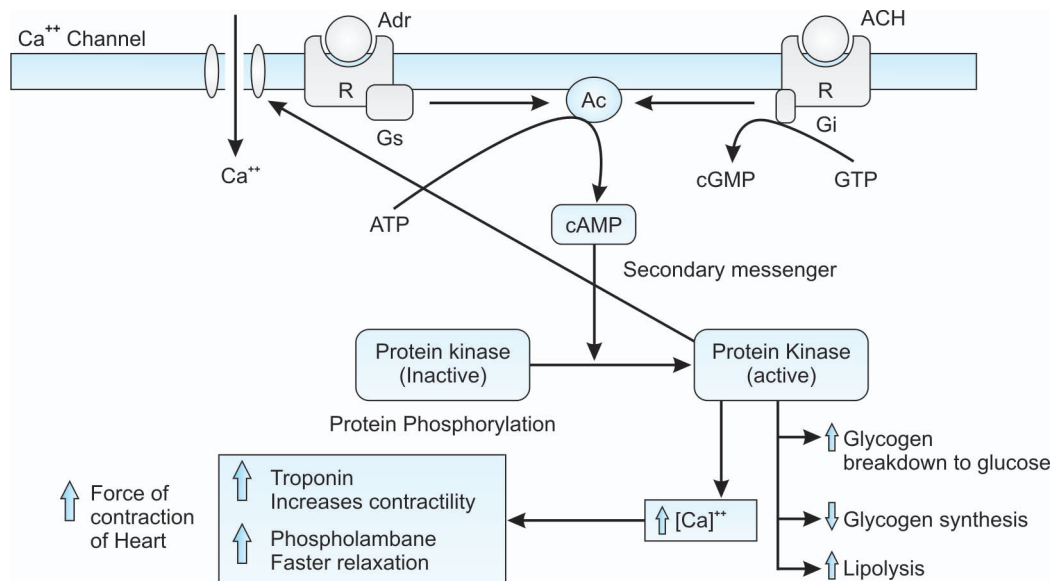


Fig. 1.6.12: The mechanism of Adenyl cyclase/Cyclic AMP system

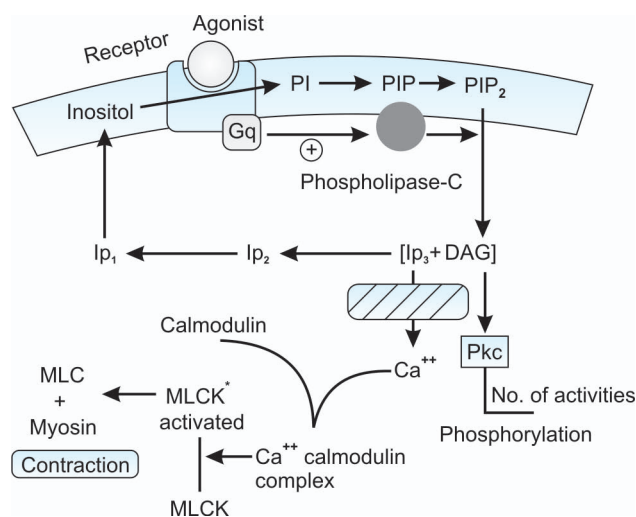


Fig. 1.6.13: The mechanism of phospholipase-C/inositol phosphate-DAG system

The regulations of ion channels: G-protein coupled receptors can control the functioning of the ion channels (e.g. Ca²⁺ and K⁺ channels) by mechanism that do not involve any second messengers such as cyclic (cAMP) or inositol phosphate (IP₃). Instead the G-protein directly interact with the channels thus affecting membrane excitability, transmitter release, contractility, etc. Cardiac muscles, muscarinic Ach receptors are known to enhance K⁺ permeability. Similar mechanism is also operates in neurons.

Type III: Kinase Linked Receptors

Examples includes: receptors for various hormones, e.g. Insulin, Growth factor, etc. (Fig. 1.6.14).

- These receptors are totally different as compared to receptors discussed previously in terms of structure and functions.

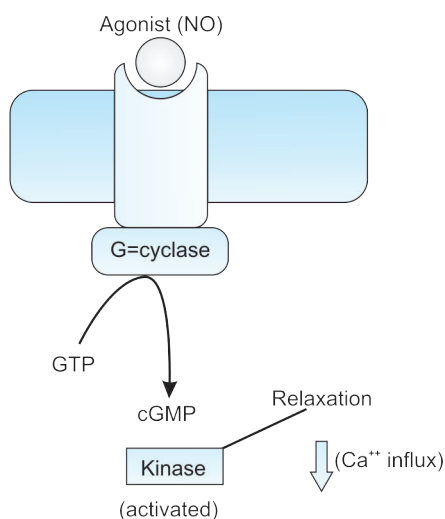


Fig. 1.6.14(a): Kinase linked receptors

- Structurally all these receptors contain large extracellular ligand binding domain connected to an intracellular (effector) domain via a α -helix.

Mechanism

- As a result of agonistic binding to the extracellular domain of these receptors leads to conformational change that results in dimerisation and activation of the intracellular enzyme domain: (e.g. tyrosine kinase domain)

This results into auto phosphorylation (TK-P) of the receptors, thus stimulating the receptors, tyrosine kinase activity toward intracellular signaling protein.

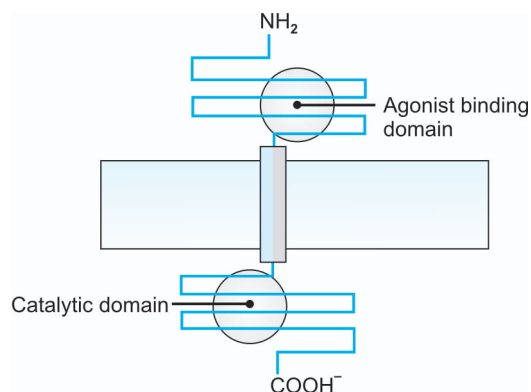


Fig. 1.6.14(b): Binding sites

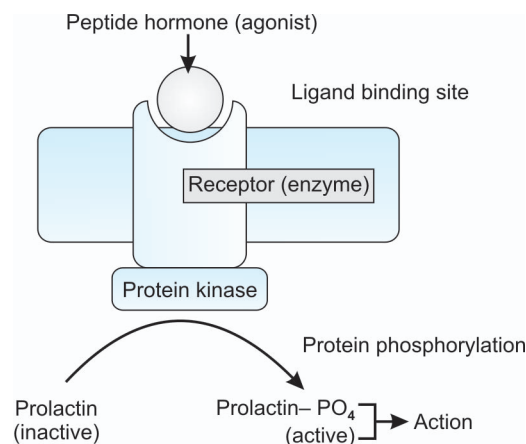


Fig. 1.6.14(c): The mechanism of kinase linked receptors

Nuclear Receptors or Type IV Receptors, which regulate gene transcription: Receptor mediated regulation of gene transcription is the characteristic property of steroids, thyroid hormones, vitamin-D, retinoic acid, etc.

These receptors are initially inactive and consist of a conserved DNA binding domain, which is attached to variable legend binding and transcriptional control domains.

On binding with specific legend (drug) they forms agonist-receptor complex, which is active. Now this agonist receptor complex moves inside the nucleus, where the DNA

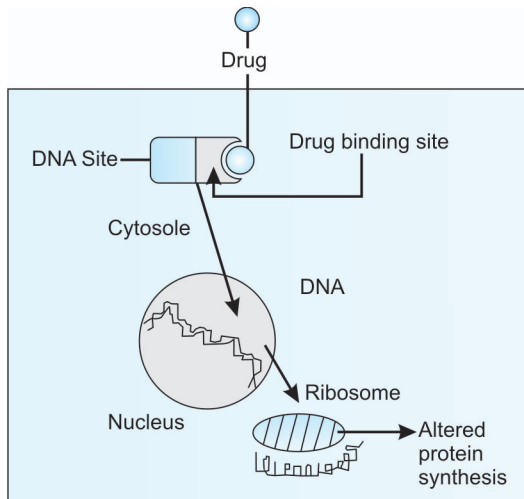


Fig. 1.6.15: Receptor mediated regulation

binding domain recognizes specific base sequences, thus promoting or repressing particular gene (gene transcription) and thereby directs the synthesis of specific proteins to regulate the activity of the target cells. The effect is slow in onset because they are produced as a result of altered protein synthesis (Figs 1.6.15 and 1.6.16).

Hormones: Cortisol, Sex steroids, Thyroid hormone, Aldosterone.

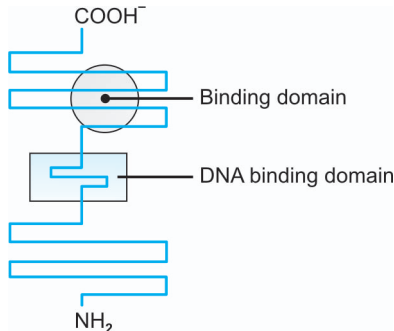


Fig. 1.6.16: Binding domain

1. Signal Transduction
 - **Heat-shock proteins** normally bind to the nuclear receptor to hold it inactive.
 - The hormone (Cortisol, Sex steroids, Tyrosine) bind to the nuclear receptor, releasing the heat shock protein.
 - The hormone-receptor complex then binds to DNA to effect transcription.
2. Cortisol stimulates **Lipocortin** → inhibit phospholipase- A_2 → inhibit synthesis of prostaglandins → anti-inflammatory properties.

Efficacy and Potency: These are comparative terms. A drug may be more efficacious or less efficacious than the other, or it can be more potent or less potent than the

other. The term '**Efficacy**' is generally used to compare therapeutic effectiveness of two drugs. Peak effect or maximum effect that can be produced with the drugs is compared. A more efficacious drug will have higher ceiling effect. The term '**Potency**' is used to compare two drugs on weight-to-weight basis.

For example, if 25 mg of drug 'A' produces a certain therapeutic response and the drug 'B' can produce the same response with 5 mg, then the drug 'B' is 5 times more

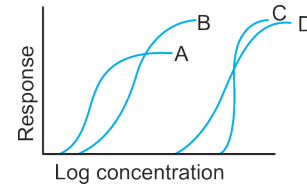


Fig. 1.6.17: DRC comparing efficacy & potency of different drugs

potent than drug 'A'. D.R.C. of a less potent drug will be on the right side of the more potent drug (Fig. 1.6.17).

Potency is of little significance in therapeutics because one can give 25 mg in place of 5 mg if the same response is obtained. **Generally** when therapeutic effect appears at a higher dose (e.g. 25 mg), quite likely the *dose dependent adverse effects* will also appear at a higher dose. A drug producing beneficial action at a lower dose, quite likely will produce adverse effects at a lower dose. **Efficacy**, reflects **capacity to generate maximum therapeutic effect, therefore is more important clinically**.

Therapeutic Window Phenomenon: Certain drugs produce optimal therapeutic effects only over a narrow range of plasma drug concentration; both above and below this range the beneficial effect of the drug is suboptimal, this is called therapeutic window phenomenon. E.g. imipramine, clonidine, glipizide, etc.

Therapeutic Index: It is the ratio of $\text{LD}_{50}/\text{ED}_{50}$. LD_{50} (Median Lethal Dose) is the dose at which 50% of the population (of experimental animals) dies. ED_{50}

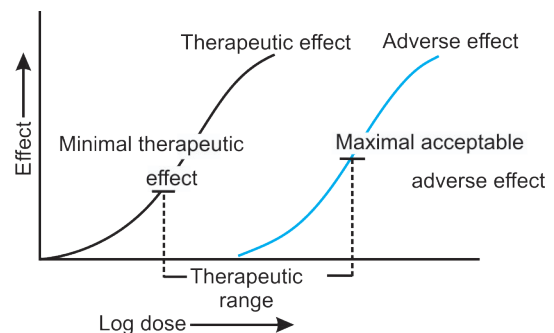


Fig. 1.6.18: DRC showing therapeutic range

(Median Effective Dose) is the dose at which the desired response is produced in 50% of the population. Both, in LD₅₀ and ED₅₀, *percent of the population responding* is considered. This is not the same as *percent of maximal response*. Therapeutic index indicates safety of a drug. Higher ratio means greater difference between the dose that is lethal and the dose that produces desired effect.

Since calculation of Therapeutic Index uses “Lethal Dose” and “Effective Dose” for 50% of population (Figure 1.6.18), its direct clinical utility is nil. However, it does indicate the ‘**safety margin**’. Clinically more relevant are the **MEC** (Minimum Effective plasma Concentration) and **MSC** (Maximum Safe-tolerable-plasma Concentration).

For example, for Aminophylline, MEC is 5 mcg/ml and MSC is 20 mcg/ml. In case of Phenytoin they are 10 and 20 mcg/ml respectively.

While using any drug, our intention is always to keep plasma concentration between MEC and MSC. Wider the **gap (margin)**, that much safer and easier it is to use a particular drug, because then it is not necessary to keep plasma concentration within a strictly narrow limit. For different drugs, requirements may vary, e.g. for how long the plasma concentration should remain above MEC or what will be the ‘peak’ plasma concentration with the loading dose (whether it will cross the MSC or not), and accordingly safety of a given dose regimen is judged.

Factors Modifying Dosage and Drug Action

Dose (Definition)

The word dose is derived from Greek, *dos*: is the amount of the medicine administered to the patient, as prescribed by the physician and expressed in terms of weight grams/milligrams/micrograms, volume in ml and standard units.

- There must be variation in the response to the same dose of a drug, in different patients and even in the same patient, on different occasions. This variation may be marked or limited, depending on a number of factors related to the patient and to the drug. These may include:
 1. Individual variation in Pharmacokinetics.
 2. Individual variations in receptor.
 3. Individual variation in endocrinal or neurological functions or tone.
- Usually this variation manifests itself as increased or decreased response to the drug and can be over come, by increasing or decreasing the dose of the drug, but occasionally, the change in response is not related to the dose or pharmacological effect of the drug, i.e. allergy or idiosyncrasy, which prevents further use of the drug.
- Many factors like pharmacogenetics, pathology, physiology, environment and drug interaction modify the doses and effect of drugs. These factors may modify the drug action qualitatively and quantitatively.
- The analgesic dose of Aspirin for headache is 300 – 600 mg while the anti-inflammatory dose for rheumatoid arthritis is 3-6 g per day. Similarly there should be prophylactic dose, therapeutic dose or a toxic dose of the same drug.

The various factors that can modify drug dosage and effects are:

1. Physiological causes

- a) **Age of the patient:** Infant and children are not small adults. Children and the elderly are often more sensitive to drug effect, as in the former, the processes of metabolism and excretion of drugs, are not well developed, e.g. chloramphenicol can

produce gray baby syndrome due to inadequate hepatic enzyme system in newborn babies, while in the latter they deteriorate with advancing age. The pharmacodynamics of drugs in children may also differ from that in adult as well. Different formulae are used to calculate doses in children, i.e.

Young's formula:

$$\text{Child dose} = \frac{\text{Age (Yrs)} \times \text{Adult dose}}{\text{Age} + 12}$$

Dilling's formula:

$$\text{Child dose} = \frac{\text{Age in years} \times \text{Adult dose}}{20}$$

- b) **Size or body weight:** During prescription writing, the average doses of the drugs are mentioned either in terms of mg/kg body weight or as a total single dose for an adult (approx. 60 – 70 kg weight).

The total single dose expression may not apply in case of either excessive obese patient or patients suffering from edema, dehydration or emaciation.

Individual dose =

$$\frac{\text{Body weight (kg)}}{70} \times \text{Total single dose}$$

- c) **Body surface area (BSA):**

Body surface area (BSA) provide more accurate basis for dose calculation. It can be calculated by:

$$\text{Individual dose} = \frac{\text{BSA (m}^2\text{)}}{1.7} \times \text{Average adult dose}$$

$$\text{BSA (m}^2\text{)} = \text{Body weight (kg)}^{0.425} \times \text{Height (cm)}^{0.725} \times 0.007184$$

Specifically anticancerous drugs can be prescribed on the basis of BSA.

- d) **Sex:** While using drugs in females, special care must be taken specially during:
- Menstruation:** Purgative must be avoided because they may produce pelvic congestion.
 - Pregnancy:** Drug given during pregnancy can affect the fetus (**Teratogenic effect**) and infant. The physiological changes that occur in the pregnant female (mother) can modify drug action and need a revision of drug dose. Drugs stimulates uterine smooth muscles are also contraindicated in the pregnancy.
 - Lactation:** Few drugs if they are given during lactation period they may adversely affect the infant and produces toxicity.

Gynecomastia, following use of certain drugs, may occurs only in males.

2. Time and place

Time and place also affect drug doses and action, for example if corticosteroid will be taken in the morning as a single morning dose causes less pituitary-adrenocortical axis suppression. Similarly if hypnotics will be taken in quite and dark room or dark place works more smoothly.

3. **Genetic variation** can lead to a decrease or increase in the quantity of drug metabolizing enzymes, in certain individual, which can account for an altered drug response, e.g. in patients with deficiency of the enzyme G-6-PD, primaquine can cause intravascular hemolysis, deficiency of plasma psedocholinesterase accounts for the occurrence of apnoea in some patients following the use of a muscle relaxant, succinyl choline, e.g. fast and slow acetylation of drugs like ioniazid and procainamide.

4. Immunological factor: (Drug allergy)

Discussed in next chapter.

5. **Psychological factors/emotional factors:** The effect of the drug (efficacy) can be modified by patient's belief, personality of the doctor and their attitudes.

- Higher dose of diazepam is required to produce tranquilization in schizophrenic patients as compared to normal individuals.
- Placebo effect of the drug: sometime inert substance (as a drug) may produce effect in patients due to faith in physician and drug.

6. Environmental factors

- Alcoholics: required more anesthetic gases for anesthesia and barbiturate for sedation as compared to non-alcoholics.

- Heavy cigarette smokers: required more or high dose of the drugs, e.g. (cimetidine) due to enzymatic induction.

7. **Route of administration:** A drug may have different effects when given by different routes, e.g. magnesium sulfate given orally acts as a laxative, applied locally acts as anti-inflammatory agent and when given IV it is a CNS depressant.

8. Rate of absorption, metabolism and excretion:

9. **Pathological states:** diseases affecting GI tract, liver, kidney and heart, can affect absorption, metabolism, excretion and volume of distribution of drugs, thus, affecting their pharmacological effect and requiring a change in the dose and/or frequency of administration. Example: in liver cirrhosis barbiturate produces prolonged effect. In renal failure, drugs which chiefly excreted by the kidney, i.e. streptomycin prove to be toxic. In CCF, clearance of lignocaine may reduced to half.

10. **Presence of other drugs:** when two drugs are given simultaneously or concurrently, they may modify the response to each other by pharmacokinetic or pharmacodynamic interaction, resulting in an increase or decrease in the response to one of the drugs, e.g. beta-receptor blocking agents potentiate the hypoglycaemic effect of antidiabetic drugs and also mask the signs of hypoglycaemia, non-steroidal anti-inflammatory drugs may blunt the hypotensive effect of antihypertensive drugs, furosamide + aminoglycosidal antibiotic can cause enhance oto-toxicity.

11. Development of tolerance and tachyphylaxis to the drug effect:

It may be congenital tolerance when some drugs are given repeatedly, the response elicited goes on reducing and in order to produce the same response, a higher dose of the drug is required. This is known as **Drug Tolerance**, e.g. alcohol, morphine, and diazepam. Rapid development of tolerance is called **Tachyphylaxis**.

- Tolerance may not develop equally to all the effects of the drug, e.g. in case of morphine tolerance is developed to analgesic and sedative effects but no to miotic or constipating effect. Tolerance is usually developed to the effect used therapeutically, but not to the toxic effect of the drug, so that as tolerance develop, the margin of safety of the drug is reduced.
- Tolerance to a drug may be **natural**, i.e. rabbits are naturally tolerant to the effects of atropine-or it may **acquired**-due to enhanced metabolism and/or ex-

cretion of drug, **pseudotolerance**. Sometimes it is due to a reduced responsiveness of the receptors, on which the drug acts-true tolerance. Body size of the patient – larger the size, more can be the dose required to produce the same effect.

- **Pharmacodynamic tolerance:** Due to long-term usage of the drug (agonist) the target cells become less sensitive (mostly because of down regulation of the involved receptors). Examples are organic nitrite, opioids, etc.
- **Pharmacokinetic tolerance:** Again if any drug is used for very long period of time there occur induc-

tions of the hepatic enzyme which result into faster metabolic degradation of the drug. Example is barbiturate.

- **Cross tolerance:** Usually tolerance develops against different drugs of the same family, but if it occurs between the different members of different but similarly resembled family then it is called cross tolerance. Example is alcohol and anesthetic agents.
- **Tissue tolerance:** If tolerance is developed to some effect only, i.e. tolerance develops to analgesic and euphoric action of morphine but not to its miotic and constipating actions.

Adverse Drug Reaction (ADR) and Poisoning

Definition

Any noxious change which is suspected to be due to a drug occurs at doses normally used in man, requires treatment or decrease in dose or indicate caution in the future use of the same drug.

All drugs can produce adverse drug effects, when administered. It depends upon pros and cons ratio, that particular drug has to be given or not.

For example: With methotrexate, risk of bone marrow suppression may be justified in treating cancer, while mild drowsiness caused by an antihistaminic in treating common cold may be unacceptable.

ADVERSE DRUG EFFECT CAN BE CLASSIFIED AS

Type I or Predictable Reaction

These are related to the pharmacological effects of a drug are quite common and often related to the dose given (Table 1.8.1). They include:

- a. Side effects:** These occur at doses used therapeutically and are due to unwanted pharmacological effects of drugs, e.g. dryness of mouth with atropine, sedation with antihistaminic, dry cough with enalapril, etc.
- b. Secondary effects:** These effects result from the indirect consequences of the primary effects of the drug, e.g. suppression of microbial flora in the GIT following the use of broad spectrum antibiotics can result in suprainfection, diarrhoea, staphylococcal or pseudomembranous enterocolitis.
- c. Toxic effects:** These occur due to over dosage or prolonged use of drugs and manifest as exaggerated pharmacological effects of a drug. They are predictable and can be prevented by taking proper precautions, e.g. gingival hyperplasia following the use of phenytoin,

peripheral neuritis following the use of isoniazide. The former can be prevented by proper oral hygiene and the latter by giving adequate doses of vitamin B6.

- d. Drug habituation and dependence:** Drugs capable of altering the mood and feeling, are liable to repetitive use to derive a feeling of euphoria to escape from the reality, social adjustment or to tide over the shock of an unexpected event. Such use of drugs, by self medication, for non- therapeutic purposes is known as abuse of drugs and repeated use of such drugs may result in tolerance, habituation and ultimately drug dependence.
- e. Drug withdrawal reaction:** Sudden withdrawal or stoppage of certain drugs can result in a type of adverse reaction, mostly manifested in the form of worsening of the clinical condition for which the drugs was being used, e.g. sudden withdrawal of beta receptors blocking agents can precipitate an attack of myocardial infarction, withdrawal of phenytoin can precipitate status epilepticus.
- f. Iatrogenic or drug induced diseases:** When certain drugs are used chronically, they can result in the production of disease, e.g. chronic use of aspirin can lead to the production of Peptic ulcer, Prolonged use of corticosteroids can cause peptic ulcer, diabetes, hypertension, cushing's habitus. Phenothiazines cause extra pyramidal symptoms (parkinsonism).
- g. Teratogenic effects:** This refers to the ability of a drug to cause congenital abnormality in the fetus, when given during the first trimester of pregnancy, e.g. cleft – palate following the use of corticosteroids, Phocomalia (absence of limbs) following the use of thalidomide in thalidomide disaster.

Type II or Unpredictable Reactions

These reactions are not related to the dose or pharmacological effect of the drug, are less common, generally more

Table 1.8.1: Adverse drug reactions

Predictable	Unpredictable
1. Side effect Occur in therapeutic doses, e.g. dry mouth, sedation syndrome, serum sickness,	1. Drug allergy Anaphylactic shock cytotoxic reaction, SJ contact dermatitis
2. Secondary effects Due to indirect consequences of primary effects of drugs, e.g. superinfections	2. Photosensitivity
3. Toxic effects Due to overdosage or prolonged use of drugs, e.g. peripheral neuritis	3. Idiosyncrasy Unexpected effects unrelated to, pharmacological effects, e.g. agranulocytosis
4. Tolerance, habituation and addiction Due to prolonged used of mood altering drugs.	
5. Drug withdrawal reactions Drug to sudden stoppage of a drug, e.g. β blockers.	
6. Teratogenic effect Fetal abnormalities when given during first trimester of pregnancy, e.g. Thalidomide	
7. Iatrogenic effect Drug induced disease, following its prolonged used, e.g. peptic ulcer, diabetes	

serious and often require withdrawal of the drug. The most important reaction of such kind is drug allergy.

- a. Photosensitivity:** It is a cutaneous reaction, resulting from drug induced sensitization of the skin to ultraviolet radiation. When the skin is exposed to sunlight while taking the drug, erythema, edema, blisters, dermatitis can occur. Drugs that can cause such reaction are demeclocycline, chloroquine.
- b. Intolerance:** It is the converse of tolerance and indicates a low threshold of the individual to the action of a drug, i.e. there occur appearance of characteristic toxic effect of a drug at therapeutic doses. Example: only few doses of carbamazepines may cause ataxia in some people.
- c. Idiosyncrasy:** It is a drug reaction, which is abnormal and is genetically determined, i.e. restricted to individuals with particular genotype only. Example Quinine/quinidine – produces cramps/diarrhea, asthma and vascular collapse in some patients.
- d. Drug allergy:** It is an immunologically mediated reaction producing stereotyped symptoms, which are unrelated to the effects of the drug or its dosage.

Usually prior sensitization is necessary and a latent period of 1-2 weeks is required after the first exposure. Allergic reactions can manifest in various forms:

- **Type –I: Anaphylactic reaction** with urticaria, angioedema, bronchoconstriction, hypotension; death can occur if immediate treatment is not given. Ig(E) reaginic antibodies are produced which get fixed to the mast cells.
- **Type –II: Cytolytic reactions**, resulting in destruction of cells leading to hemolysis, thrombocytopenia, agranulocytosis, aplastic anemia. Drug + component of a specific tissue will act as antigen.
- **Type –III: These are delayed reactions**, which manifest as rashes, serum sickness, Stevenson-Johnson syndrome (erythema multiform, arthritis, nephritis, myocarditis). These are mediated by circulating IgG.
- **Type –IV: Contact dermatitis.** These reactions are mediated through production of sensitized T-Lymphocytes carrying receptor for antigen.

Treatment of drug allergy:

Antihistaminic drug

In case of anaphylactic shock or angioedema:

- Adrenaline (0.5 mg sc) state
- Antihistaminic +
- Glucocorticoids

Mechanisms of Variation in Drug Responsiveness

Four general mechanisms may be responsible for variation in drug responsiveness among patients or within an individual patient at different times:

- 1. Alteration in the concentration of the drug** that reaches the receptor due to variation in the rate and/or extent of drug absorption or drug distribution or metabolism or clearance, thus altering the amount of the drug that reaches the receptor. Such differences can be predicted on the basis of age, weight, sex, disease state, liver and kidney function and by testing for the presence of genetic differences, e.g. pseudo ChE, G-6- PD deficiency, etc.
- 2. Variation in the concentration of the endogenous receptor legend:** This mechanism is responsible for variation in the responses seen to antagonists, e.g. beta-receptor blocking agents are more effective in slowing the heart rate in patients whose endogenous catecholamine levels are elevated, as in pheochromocytoma, but they may not reduce resting heart rate. Similarly, a partial agonist like saralasin, will lower blood pressure in patients with raised angiotensin II levels, while it will cause a rise in BP in patients who produce low amounts of angiotensin.
- 3. Alteration in the number or function of receptors**—continuous exposure of the receptors to an agonist can result in down – regulation of receptors with the development of tolerance to the effect of drug. Conversely exposure to an antagonist can cause up-regulation of receptors with exaggerated response to the endogenous ligand, resulting in exacerbation of the disease, following abrupt withdrawal of the drug. Thyroxine, is known to increase beta-adrenoceptors in the heart accounting for the tachycardia seen in patients with thyrotoxicosis and may account for the effectiveness of beta-blockers in controlling the symptoms of hyperthyroidism.
- 4. Other mechanisms**
 - a. Differences in the severity and pathophysiology of the disease can account for variation in the degree of response observed, as is seen in congestive cardiac failure, diabetes mellitus, etc.

- b. Activation of compensatory mechanisms may account for the reduction in the response to a drug, following its prolonged use, e.g. in hypertension.

Teratogenicity

It refers to capacity of a drug to cause fetal abnormalities when administered to pregnant mother by crossing through placenta. Example – thalidomide ————— Phocomelia (Seal like limbs), other drug includes: Anti-epileptic/Androgen/Progestin).

Carcinogenicity and Mutagenicity

It refers to the capacity of a drug to cause cancer and genetic defect respectively for example radioisotopes.

DRUG DEPENDENCE

Drug dependence is a state in which there occurs alteration in the mood and feelings are liable to repetitive use to obtain euphoria, withdrawal from reality and social adjustment etc.

Classification**Psychological dependence**

It is a condition in which individual starts believing that normal (optimal) state of well being is achieved only through the action of the drug – lead to self medication.

Physical dependence

It is an altered physiological state produced by repeated administration of a drug. Discontinuation of the drug results in a characteristic withdrawal (abstinence) syndrome discussed previously. Example – Morphine.

TOLERANCE

Tolerance means requirement of higher dose of the drug to produce the same response. **It can be:**

- a. Natural tolerance** – example: rabbit is tolerant to atropine
- b. Acquired tolerance** – On repeated use of drug tolerance can be produced.

Tachyphylaxis: It means rapid development of tolerance.

Drug resistance

It refers to unresponsiveness (tolerance) of a microorganism to microbial agents. It is discussed in detail under heading antimicrobial agents.

POISONING

The poisoning and its treatment is studied under the heading Toxicology.

Toxicology: It is the branch of science, which deals with the study of untoward effects of any substance including drug toxicities or poisoning, whether because of internal or external exposure, and relating to both immediate and long-term implications in the realm of human ecology.

Management of drug overdoses and poisoning

Management principles

- Identification of the drug is very important which should be done by:
 - Proper history taking.
 - Observing physical findings.
 - Chemical analysis of the vomitus or agent.
- A keen knowledge of the drug pharmacology specially its pharmacokinetic and pharmacodynamic aspects + toxic effects is essential.
- Intensive support care:
 - Assess the adequacy of ventilation and oxygenation.
 - Establish and maintain a clear airway by:
 - Orotracheal or nasotracheal intubation.
 - Positive pressure ventilation + O_2
 - Management of pulmonary edema.
 - Fluid and electrolyte maintenance.

Prevention of drug absorption

- Forced emesis: Syrup epicac 30 ml PO followed by at least 16 oz water.
- Gastric lavage: Gastric irrigation with normal saline (300 ml at a time) and lavage.
- Activated charcoal or universal antidote: Universal antidote is made up of three components a) activated charcoal or burned toast b) tannic acid or tea, and c) milk of magnesia. In a recent study it was found that activated charcoal alone is equally effective as the combination.

- Administering cathartics, per orally, i.e. Mg – citrate.

Maintenance of circulation

- Assess the adequate CVS status by following vital signs; ECG and by monitoring CVP.
- Hypotension can be treated by: Dopamine 2–50 mcg/kg/min.
- Hypertension is uncommon and if occur can be treated by nifedipine, Na-nitroprusside, beta-blockers and diuretics.
- Controlling, dysarrhythmias.

CNS depression

- Immediate 50% dextrose
- Supportive care

Convulsion can be treated by—Diazepam Hypothermia or Hyperpyrexia should be immediately treated.

- Hyperpyrexia Should be treated with cold sponging, paracetamol, etc.
- Hypopyrexia Should be treated with heat preservation.

Removal of absorbed drug

- Forced alkaline diuresis or
- Forced acid diuresis depending upon the nature of the poison.
- Dialysis
- Hemoperfusion, in case of life threatening poisoning.

Administration of selective or specific antidotes

Poison	Antidote
• Methanol	Ethanol
• Diazepam	Flumazenil
• Paracetamol	Methionine or N-acetyl cystine
• Morphine	Naloxone
• Iron	Desferrioxamine
• Copper	Penicillamine or BAL (Dimercaprol)
• Lead	EDTA or BAL

Drug Interactions

Definition

Drug interaction may be defined as the modification of the pharmacological effect of one drug by the presence of another drug when two or more drugs are administered at the same time, they may exert their effects independently or they may interact and thereby enhance, reduce, or delay the effect of each other, such interactions are called **drug interaction** or therapeutic incompatibility. It is distinguished from drug-food interaction.

Effect of drugs can be potentiated or reduced when two or more drugs are administered concurrently in combination;

1. When the presence of one drug enhances the effect of other drug, the phenomenon is known as **Synergism**.
2. When effects are reduced the phenomenon is called as **Antagonism**.
3. When the effect of the combined drug is just equal to the sum effect of the individual drugs it is called as **Additive effect**.

Synergism: It enhances therapeutic efficacy

Antagonism: It reduces therapeutic efficacy.

- Risk of ADR (Adverse Drug Reaction) is increased with multiple drug regimens.
- A drug-drug interaction (DI) is likely to have therapeutic consequences (TDI) if it alters the
 1. Concentration of a drug with a steep dose-response relationship
 2. Drug response for a condition which are unstable (e.g. cardiac arrhythmias, epilepsy)
 3. Vital processes in the body.

Drugs usually involved in TDIs include anticoagulants, cardiac glycosides, anti-arrhythmias, sympathomimetic amines, antihypertensive, anticonvulsants, oral hypoglycemic, cytotoxics, etc. (Risky drugs)

Phase I enzymes are cytochrome P450s, phase II enzymes are conjugative enzymes.

MAJOR MECHANISMS OF DRUG INTERACTION

A. Drug interactions outside the body

Use of wrong vehicle for infusion

No drug should be added to blood, plasma, amino acid solution, fat emulsions, sodium-bicarbonate solutions, mannitol and heparin solution.

Addition of drug to an infusion

Drugs should be added to infusion containers only when constant plasma concentration are needed or when the administration of a more concentrated solution would be harmful.

B. Drug interactions inside the body

PHARMACOKINETIC

Absorption

Interference with gut absorption

1. Complex formation in gut
Example: Cholestyramine binds many drugs: $\text{Ca}^{++}/\text{Mg}^{++}$ antacids complex with iron, tetracycline, quinolones
2. Delayed/accelerated gut emptying
Example: anticholinergics delay gastric emptying and therefore delay drug absorption
3. Changes in gut flora
Example: antibiotics interrupt enterohepatic recycling of the estrogen component of oral contraceptives, causing contraceptive failure: Erythromycin prevents bacterial inactivation of digoxin in the gut, increases bioavailability, plasma digoxin levels rise 50%.

Alteration in first pass metabolism

(Note: high clearance drug have > 30% extraction from hepatic blood.)

A drug that inhibits hepatic metabolism will increase bioavailability of high clearance drug (provided it is metabolized by the enzyme(s) inhibited) and vice-versa.

Examples:

1. Cimetidine inhibits CYP-450s, therefore doubles oral propranolol bioavailability
2. Phenytoin induces enzymes, therefore decreases felodipine bioavailability
3. Acute alcohol intake inhibits a CYP, therefore amitriptyline bioavailability is higher

Distribution**Drug-protein binding displacement****In plasma**

1. The drug displaces another drug from a binding site on plasma protein leading to:
 - Transient rise in $f(u)$ (unbound concentration) of displaced drug.
 - Compensatory rise in drug clearance
2. Therefore a new steady state $f(u)$ is reached that is similar to the initial level - therefore this is usually clinically unimportant (unless the transient rise in $f(u)$ is toxic)

Example of clinical importance:

- 99% of warfarin binds to albumin
- NSAIDs bind to same site, and therefore displace albumin, causing a transient rise in warfarin, which can be dangerous while it lasts

In tissue*Example:*

- Digoxin binds to intracellular sites in muscle
- Quinidine displaces digoxin from tissue sites, leading to an 80% rise in plasma digoxin levels

Elimination**Enzyme induction**

If this metabolic route is a major pathway of elimination, drug kinetics will change (reduce C_{ss} and $T(1/2)$) and therefore drug response will change

- Enzyme induction takes about 2 weeks to develop, and on cessation of inducer, about 2 weeks to revert to normal

Examples:

1. Smoking causes 100% increase in clearance of theophylline
2. Phenobarbital and rifampicin cause 200% increase in clearance of warfarin
3. Carbamazepine causes 200% increase in clearance of clonazepam
4. Chronic alcohol

Enzyme inhibition

(drugs that reduce hepatic blood flow also inhibit metabolism of high clearance drugs)

- If this metabolic route is a major pathway of elimination, drug kinetics will change (increase C_{ss} and $T(1/2)$) and therefore drug response will change
- Enzyme inhibition is immediate, and on cessation of inhibitor, reversion to normal is immediate.

Examples:

1. Metronidazole decreases clearance of warfarin by 40%
2. Cimetidine decreases clearance of phenytoin by 35%
3. Propranolol decreases clearance of lignocaine by 50% (by reducing hepatic blood flow)
4. Omeprazole decreases clearance of warfarin

Examples with regards to enzymes other than cytochrome P450s*Example 1: Allopurinol*

- Is a xanthine oxidase inhibitor (used as an anti-gout agent)
- Also inhibits metabolism of cytotoxic agent 6-mercaptopurine (6-MP).
- Therefore, concurrent use of allopurinol and 6-MP leads to elevated plasma levels of 6-MP and toxicity.

Example 2: Disulfiram

- Inhibits aldehyde dehydrogenase
- Therefore is used to give alcoholics a nasty "aldehyde reaction" when they take alcohol

Alteration of liver blood flow

For high first pass clearance drugs only, a fall in liver blood flow will cause a clear reduction in systemic clearance

- Example: *Lignocaine toxicity can occur when patients are given a beta-blocker which reduces liver blood flow.*

Interference with renal excretion

Interference can occur if there is competition for tubular secretion; this will only be clinically significant if drug has a narrow therapeutic ratio and a large fraction is excreted unchanged

(Note also sometimes interactions with tubular reabsorption)

Example 1: Penicillin

1. Probenecid is a competitive inhibitor for tubular secretion
 2. Once (years ago when penicillin was not readily available) probenecid was used to reduce dose requirements by 80%
- *Example: Procainamide*
 1. Procainamide competes with cimetidine for renal tubular excretion through the organic cation transporter
 2. Using both at once may result in procainamide toxicity

- *Example: Lithium*
 1. Diuretics and NSAIDs both enhance proximal tubular reabsorption of Na^+ and Li^+
 2. Therefore these elevate Li^+ levels

PHARMACODYNAMIC

(may occur at receptor, cell or physiological level)

Synergistic effects

- Commonly used therapeutically; examples of synergy used therapeutically:
 1. *Parkinson's disease*: L-dopa + monoamine oxidase B inhibitor
 2. *Hypertension*: vasodilator + negative inotrope
- Problems can occur, the following show synergy:
 1. CNS sedatives, e.g. alcohol + barbiturates
 2. Hypertension - monoamine oxidase A inhibitor + sympathomimetic
 3. Digoxin toxicity - diuretics that cause hypokalemia + digoxin

Antagonistic effects

- Occasionally used therapeutically to reduce a side-effect; example:
 1. Benzhexol (anticholinergic) used to treat Parkinsonism induced by chlorpromazine (tranquiliser)
- Problems can occur:
 1. NSAIDs reduce antihypertensive efficacy (reduce renal sodium excretion)

CLINICAL APPROACH TO DRUG-DRUG INTERACTIONS

1. Predict and avoid if possible, that is
 - Become familiar with drug TDIs
 - Take full drug history (including alcohol, smoking)
 - Avoid multiple drug use if possible
 - If multiple drugs need to be used, select drugs to avoid TDIs
2. If unavoidable, carefully monitor drug response

Rational Prescription Writing in Dentistry

What is required for PROPER (RATIONAL) use of the Drug ?

→ Knowledge about the Drugs

1. Actions, mechanism of action
 2. Harmful effects
 3. Pharmacokinetics
 4. Method of administration
- Selection of the most suitable drug or drug formulation.

After Selection, what will you do?

Write a Prescription !

This topic (prescription writing) will be discussed under the following headings:

- A. Definition
- B. Types of prescription
- C. Format and parts of prescription
- D. Drug nomenclature
- E. Abbreviations
- F. Metrology (Weights and Measures)
- G. Label
- H. Drug formulations

A. What is a Prescription ?

Definition: It is a written order by the physician (dentist) to the pharmacist containing instruction regarding the name of the drug(s), dose, preparation and dispensation and also instructions to the patient regarding mode of administration of the drug.

B. Types of Prescription

- | | | |
|-------------------|---|----------------|
| 1. Compounded | { | Official |
| | | Extemporaneous |
| 2. Pre-compounded | { | Official |
| | | Extemporaneous |

Compounded: The dose and the composition of the preparation is decided by the doctor (dentist) and

according to the doctor's advice, the pharmacist prepare the medicament. These are non-official or extemporaneous preparation. When the composition is according to any official publication (see later) it is called Official preparations.

Pre-compounded: These are the preparations marketed by the pharmaceutical companies and the composition is either as per the Official publications or the companies decide the composition of their own product. These preparations are available *ready made* and do not require '**compounding**' by a pharmacist. These days '**Pre-compounded**' preparations are used almost exclusively. Because of a very large number of formulations and combinations available in the market, the selections becomes really very difficult. The physician should satisfy himself about the merits and demerits of the formulations. He has to be sure of presence and absence of any particular drug, dosage and bioavailability in the product he chooses. The physician (dentist) should also consider the cost of the medicament, particularly when duration of the therapy is longer. (Remember in case of the rest of the commodities it is the choice of the customer to choose costlier or cheaper goods but in medical profession the doctor is executing the choice for the patient and hence this aspect should be born in mind).

The '**Official**' formulations are described in the official publications like Formularies, Pharmacopoeia or Pharmaceutical Codex. These official publications give descriptions about the drugs, their physical and chemical characteristics, methods of standardization, doses, dosage forms, etc. Indian Pharmacopoeia (**IP**); British Pharmacopoeia (**BP**); United States Pharmacopoeia (**USP**); National Formulary (of America) (**NF**); National Formulary of India (**NFI**); British Pharmaceutical Codex (**BPC**)—are the examples of such publications. These publications are under authority of Government body or recognized societies.

Under the regulations of the FDCA (Food and Drug Control Administration - of India) certain drugs are made available to the patient only on the prescription of the qualified doctor. These are called **Schedule 'H' drugs**. Although, certain drugs meant for common ailments are available without the prescription. Such preparations are called Over The Counter (**OTC**) preparations, e.g. many preparations of aspirin, paracetamol are available for treatment of headache, bodyache, etc. Some dangerous drugs like barbiturates and amphetamines (Schedule "**X**" Drugs) are not easily dispensed. They require prescription in two copies; one copy remains with the pharmacist and the other copy is for the patient. This is to avoid misuse of these dangerous compounds. Sale of opioid and other narcotic drugs is regulated by "Narcotic Drugs and Psychotropic Substances Act '85". These drugs can be sold only by special license holders.

When a patient is admitted in the ward, the instructions are directed to the nursing staff rather than to the patient. In either situation (Out-door or In-door), the prescription carries legal importance.

C. Prescription writing involves a typical format: Parts of the Prescription (Fig. 1.10.1)

Superscription: Superscription consists of name of the dentist/doctor, qualification, address, date of writing prescription on the right upper corner. On the left side, name of the patient, age, sex and address are written. This is followed by symbol (**R_x**). It represents prayer to God Jupiter. It is pronounced as Recipe. This means "You (as patient) take (this medicament in the name of God, who may cure you)." Superscription identifies the doctor and his qualification and is important from medicolegal point of view. Date on the prescription prevents repeated self medication. Identity of the patient, etc. prevents confusion and a knowledgeable pharmacist can even point out any error in dose especially for children.

Inscription: Inscription is the body of the prescription containing name, formulation and dose of the drug. There may be more than one drugs or ingredients of the inscription. They may be

Basis: It is the active or principal drug responsible for main action.

Adjuvant: This aids or increases the action of the principal ingredient. It is not always present.

Corrective: It modifies or corrects the undesirable effect of the basis or adjuvant. It makes preparation palatable by adding flavoring, sweetening or coloring

agents, e.g. sugar coating for bitter chloroquine tablet. It is not always present.

Vehicle: This is a medium used as solvent in the solution, or to dilute the mixture. They are pharmacologically inert. They may be liquids (for mixtures) or semi-solids (for creams, ointments - known as bases) or solids (for tablets). In a particular prescription all four kinds of ingredients may not be present. There may be more than one active ingredients.

- a. An example of prescription of **precompounded** medicament:

Dr. Treat Everything BDS. Reg No: 010101 101, Heaven's Way Surat Date February, 1, 2010 For, Mr. Ever Tooth Trouble, Age 30 111 Obstacle Road Surat, R_x Cap Ampicillin (I.P.) 250 mg. Dispense 30 capsules 2 caps to be taken every 6 hourly for 5 days. <i>Follow up after 5 day.</i> Signature of Doctor
--

- b. Following is an example of extemporaneous (**compounded**) prescription:

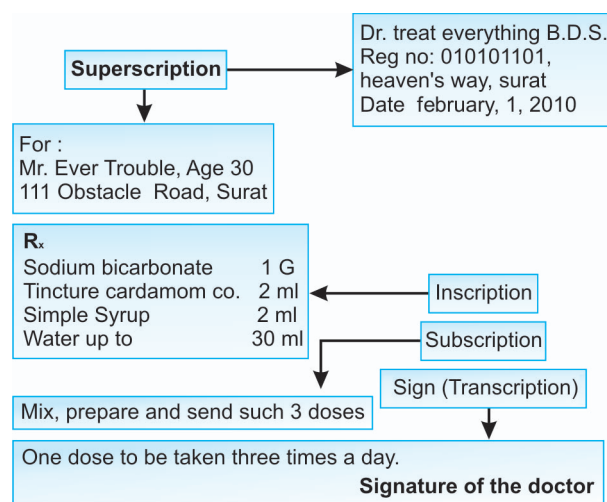


Fig. 1.10.1: Parts of prescription

Subscription: Subscription contains direction to the pharmacist regarding preparation of the drug, e.g. mix and prepare a mixture, send such 10 tablets, etc.

Signa (Signature) (transcription): This is not to be confused with signature of the doctor at the end of the prescription. Signa is the direction to the patient about the use (mode of administration) of the drug. Here the instructions are to be very clear without any confusion. Earlier there used to be a lot of Latin abbreviations in the direction to the patient. That should be avoided and the instructions should be in simple language, preferably in patients' own language. Avoid using words "take as directed" or "take as necessary". Clear message such as 'one dose to be taken three times a day' or 'one tablet to be taken at bed time' should be written. Finally, there is the signature of the doctor. This also carries **medicolegal importance**.

Dentist [doctor's] signature carries an importance as prescription is a legal document and should bear the signature of the doctor. Try to write the prescription on a single page and sign at end on the same page.

D. Names of the drugs: Drugs are known by various names. For example acetyl salicylic acid is a chemical known as Aspirin and is marketed by various companies under different names (like Disprin by Reckitt & Colman). Here acetyl salicylic acid is the chemical name, Aspirin is the official name, Disprin is the proprietary or brand name.

E. Abbreviations: Here is list of some abbreviation which are in common use. Their use should be discouraged.

a.c.	(Ante cibum)	before food
aq.	(Aqua)	water
b.i.d.	(Bis in die)	twice daily
c	(Cum)	with
et	(Et)	and
h.s.	(Hora somni)	at bed time
mist	(Mistura)	a mixture
noct	(Nocta)	at night
p.c.	(Post cibum)	after food
q.i.d.	(Quarter in die)	four times a day
q. 6 h.	(Quaque 6 hora)	every six hours
q.s.	(Quantum sufficient)	as much as may be required
st	(Statum)	immediately
s.o.s.	(Si opus sit)	when required
t.i.d.	(Ter in die)	thrice daily

F. Weights and Measures: (Metrology)

While writing a prescription the quantity of the drug to be dispensed is expressed in different ways. There should

not be any chance of misunderstanding and the quantity should go correctly.

Metric system is used in almost all scientific work and it should be followed. Earlier pothecaries' system was followed. Metric conversion tables and some Apothecaries' equivalents are as follows:

Metric System

1 Kilogram	= 1000 gram (g or gm)
1 Gram	= 1000 milligram (mg)
1 Milligram	= 1000 microgram (mcg or mg)
1 Microgram	= 1000 nanogram (ng)
1 Nanogram	= 1000 picogram (pg)
1 Picogram	= 1000 femtogram (fg)
1 Femtogram	= 1000 attogram (ag)
1 Liter	= 1000 milliliter (ml)
1 Milliliter	= 1000 microliter (μl)
1 Milliliter (ml)	= 15-20 drops (60 drops/ml in micro-drip set)
1 drop	= 0.065 ml (Water)

Imperial system

1 Ounce (Oz)	= 28.4 gm
1 Fluid Ounce (fl.Oz)	= 29.57 ml
*1 Pint (p)	= 473.2 ml
1 Kilogram (kg)	= 2.2 pounds

* The word 'pint' is commonly used to indicate one 'container' of Intravenous fluid quantity of which may vary from product to product.

Domestic measures

1 Teaspoonful	= 4 ml
1 Dessert spoonful	= 8 ml (approx.)
1 Tablespoonful	= 15 ml
1 Tumblerful	= 240 ml

Quantities of the drug can be written as

Aspirin	0.3 g	Aspirin	300 mg
Paracetamol	0.5 g	Paracetamol	500 mg

The same can be written as

Look at the following way of writing

	G or ml	
Magnesium sulphate	8	0
Light magnesium carbonate	1	5
Oil of peppermint	0	1
Syrup	4	0
Water up to	30	0

Here, instead of decimal point a decimal line is drawn. Depending on the solid or liquid, unit of Gram or milliliter

is to be understood. On the right hand of the decimal line fractional quantities are represented.

If you write a dose of digoxin using decimal line, it will look like:

- i. Tab. Digoxin “000025” or “0.00025” which may appear confusing as compared to
- ii. Tab. Digoxin 0.25 mg.

Use of second option is obviously more convenient and has clarity.

G. Label: There should be proper instruction given to the patient in writing along with the drug. This is given in the form of label. In case of compounded preparations the chemist/pharmacist has to make the label. In case of precompounded preparation the drug houses print the instructions. **Label should clearly mention the quantity of the individual dose and frequency of administration.** Special instructions like “**SHAKE THE BOTTLE BEFORE USE**”, “**FOR EXTERNAL USE ONLY**”, etc. should be mentioned in the bold letters at the top.

When medicaments are meant for external use they should be dispensed in a special type of the bottle. They are wide mouth or colored bottles (amber colored or blue colored). Some times they are ribbed so that one can identify the bottle even by the touch and thus mistake of taking the drug internally can be avoided.

H. Drug Formulations: This topic was discussed in 1st chapter pharmacokinetics.

Rational therapeutics and rational prescription writing:

The word therapeutics means “**to care for**” (to treat). Under the heading of rational therapeutics therefore, we consider the treatment to be offered to the patient. The word ‘**rational**’ signifies that the treatment should be based on some sound reasoning to give maximum benefit to the patient. For treatment, drugs may or may not be required. There may be use of non-drug remedies like giving rest to the body or part of the body, application of hot or cold fomentation, etc. (Table 1.10.1).

Table 1.10.1: Drug schedules in India

According to Drug and Cosmetic Act, in India following “Drug Schedules” are implemented for general practitioners, which are prescription related schedule:

1. H – Schedule Drugs:

This includes the drugs sold by the Medical Shoppes on production of written prescription given by registered practitioner (Doctor)

2. W – Schedule Drugs:

This includes very few drugs which are marketed as OTC (over the counter drugs) under generic name only, i.e. Analgin, Aspirin, etc.

3. X – Schedule Drugs:

This includes drugs having addiction liability. Strict direction is required regarding their labeling, storage, prescription and sale of such drugs.

4. G – Schedule Drugs:

This includes some dangerous drugs. These drugs should be taken under medical supervision.

5. J – Schedule Drugs:

It includes list of drugs which should not claim prevention or cure of the disease, i.e. HIV and atherosclerosis.

6. K – Schedule:

Condition under which registered medical practitioners and Hospitals are exempted from provision as given in chapter IV of Drugs and Cosmetic Act 1940 of India.

7. Schedule – C:

For special products like vaccines, sera, insulin and antibiotics.

8. Schedule – F:

For ophthalmic preparations

Gene Therapy

DEFINITION

Gene therapy refers to introduction of functional gene (nucleic acid) into target cells to replace or supplement defective gene.

- i. This therapy can impart new function to a cell. It is a new concept in its preliminary stage. However, it has yielded limited success to date and remains as yet an investigational treatment.
- ii. Gene therapy is now recognized as a potential treatment strategy for curing a wide range of disorders like cancer, immunological disorders, cardiovascular diseases, neuro-degenerative disorders, diabetes, AIDS, thalassemia, infections, etc.

Forms of Gene therapy: Gene therapy can be used in following forms:

1. **Germ-line gene therapy:** This allows transmission of modified genetic information to the next generation and is not currently accepted as an appropriate therapeutic approach, for ethical reasons.
2. **Somatic gene therapy:** It refers to modification of the somatic, differentiated cells of the body, in an effort to correct inherited diseases like cystic fibrosis and acquired disorders like rheumatoid arthritis or malignancies.
3. **Genetically engineered proteins:** Is another form, closely related to gene therapy in which cloning of human genes allows pure, uncontaminated proteins to be produced in large quantities. These proteins can be modified by recombinant DNA technology to enhance their therapeutic benefit. Such proteins include:
 - Hormones-like insulin, growth hormone and gonadotrophins (FSH and LH) used in the treatment of diabetes mellitus, growth hormone deficiency and for induction of ovulation, respectively.
 - Blood cell stimulating factors-erythropoietin, granulocyte stimulating factor (GSF), granulocyte

macrophage CSF, and thrombopoietin-used in anemia, neutropenia, thrombocytopenia.

- Interferons (IFNs) and interleukins (ILs-2)-used to treat hepatitis C, Multiple sclerosis, Renal cell carcinoma and for Immunosuppression in renal transplantation.
- Tumor necrosis factor alpha receptor used to treat rheumatoid arthritis.
- Clotting factors-VIII and IX used in hemophilia A and B.
- Thrombolytic agents-Tissue plasminogen activator and antithrombotic agent hirudin, used in myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis.
- Recombinant antigens-used for hepatitis B vaccines.
- Humanized monoclonal antibodies-used for the treatment of breast cancer (epidermal growth factor receptor), prevention of platelet aggregation after angioplasty (GpII/IIIa receptor) and bronchial asthma (IgE antibodies).

Goals of gene therapy: These vary, depending on the nature of the disease being treated. For an inherited disease like hemophilia life long replacement of the missing gene, secreting the clotting factor, can ameliorate the disease or reduce the need for exogenous treatment.

1. Long-term gene delivery involves modification of the host chromosomal sequences, which allows normal inheritance and stability of the delivered gene.
2. Transient gene expression can be used to treat a variety of diseases like:
 - i. For killing cancer cells,
 - ii. Providing chemoprotection to normal cells,
 - iii. Preventing coronary restenosis,
 - iv. Providing DNA based immunization and
 - v. Impairing viral replication.

Administration of gene therapy: Gene therapy can be administered *ex vivo* or *in vivo*:

1. **Ex vivo gene therapy** is given for conditions in which cells can be harvested, manipulated in tissue culture and then reintroduced, into the patient, e.g.
 - i. In Adenosine Deaminase Deficiency (ADD), Severe Combined Immunodeficiency, (SCID), the missing ADD gene is integrated in patients T-Lymphocytes, which are then reintroduced, after genetic manipulation.
 - ii. In familial hypercholesterolemia, the LDL receptor gene is inserted into patients liver tissue (hepatocytes), in cell culture and the modified cells are then infused back through the portal vein.
 - iii. Saphenous veins are treated with oligonucleotides designed to block vascular smooth-muscle cell proliferation, before using them for coronary artery by pass graft.
2. **In vivo gene therapy**, in this the missing genes are introduced into the patient using viral vectors, e.g.
 - i. In Cystic fibrosis, viral vectors are administered to the lung by aerosol.
 - ii. In Factor IX deficiency, hemophilia B, the gene is introduced into the muscles.
 - iii. Tumors can be injected with viral vectors expressing cytotoxic genes or immunotherapies.

Gene Transfer Vectors

1. A vector or vehicle is used to transfer a gene to an appropriate cell.
2. When a gene is to be added (transgenic) to supply a missing function in the recipient cell, the vector contains DNA sequences encoding a therapeutic protein, under the control of transcriptional regulatory elements necessary for gene expression (Fig. 1.11.1).
3. The gene is expressed from an ectopic location as against its normal chromosomal position.
4. Another approach is to correct mutant genes at their normal chromosomal location through gene targeting. This approach is difficult to achieve as it requires more technical skill.

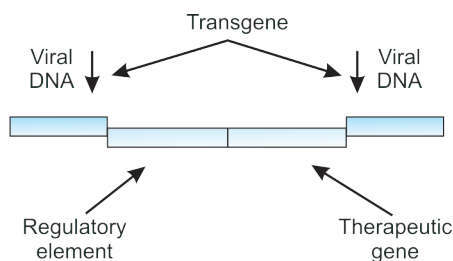


Fig. 1.11.1: DNA sequence in a vector

5. Vectors that integrate into host chromosomes are ideal for life long expression of genes, while Un-integrated (episomal) vectors are good for transient gene delivery. Two classes of vectors are used to transfer nucleic acids into cells-*viral vectors* and *non-viral vectors*.

- **Viral vectors:** In this viruses are genetically engineered, so that they can transfer exogenous nucleic acids into cells through a process called transduction (Fig. 1.11.2).

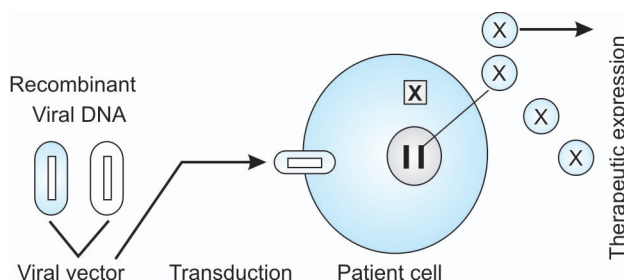


Fig. 1.11.2: Viral vector for gene transfer

Various viral vectors used for gene transfer include:

- i. **Retroviral vectors:** Based on murine leukemia viruses (MLVs). These are widely used because of their ability to integrate with host chromosomes, offering the potential for life long transgene expression. However, complement-mediated vector particle inactivation has limited their use to *ex vivo* application. New retroviral vectors include lentiviral vectors and spumaviral vectors.
- ii. **Adenoviral vectors:** These vectors remain episomal or extrachromosomal and so mediate transient gene expression. Their use is limited by their short duration of expression and their ability to evoke an acute inflammatory response.
- iii. **Adeno-associated virus vectors (AAV):** These are paravoviruses, which require a helper virus, as adenovirus, to mediate a productive infection. Though, they have a small packaging capacity, limiting the size of exogenous DNA that can be incorporated, they transduce cells both through episomal transgene expression and chromosomal integration. They can also be used to modify homologous chromosomal sequences through gene integration, an important strategy for correcting genetic mutation. They cause little immune or inflammatory response, except for generation of neutralizing antibodies, which can limit readministration. They are currently undergoing clinical trials for the treatment of cystic fibrosis and hemophilia.

iv. Other Viral vectors: Herpes viruses, double stranded RNA viruses, autonomous parvoviruses, papoviruses and hybrid viruses (mixture of components from more than one virus) are under development.

- **Non-viral vectors:** These consist of DNA/RNA complexes with lipids, carbohydrates, proteins and or other synthetic chemicals. They offer improved safety, by avoiding viral components, but their gene transfer efficiencies are much lower than viral vectors, they do not integrate and the majority of DNA molecules that enter the cell are rapidly degraded, so that only transient gene expression can be achieved. They have been used for vaccination with specific antigenic genes, *ex vivo* treatment of vessels used for coronary artery by-pass graft and transient immune modulation for the treatment of cancer.

Applications of gene therapy: Clinical application of gene therapy is still at an experimental stage. The various conditions in which studies are going on are:

- a. Respiratory system:** Treatment of cystic fibrosis.
- b. Retina:** Retinitis pigmentosa.
- c. Liver:** LDL receptor gene as a treatment for familial hypercholesterolemia.
 - i. Hepatocyte gene transfer to treat urea cycle disorders, aminoacidopathies, disorders of carbohydrate metabolism and lysosomal storage disease.
- d. Hemopoietic system:** X-linked severe combined immunodeficiency with MLV vectors encoding cytokine receptors.

- i. Chronic granulomatous disease in which there is failure of granulocytes and monocytes to generate hydrogen peroxide for bacterial killing.
- ii. Stem cell gene therapy in the treatment of hemoglobinopathies.
- iii. Lymphocyte gene transfer in ADA deficiency.
- iv. Factor X deficiency.
- v. Hemophilia A and B.

e. Cardiovascular system: *Prevention of restenosis after angioplasty by vascular wall gene delivery.*

- i. IM injection of DNA vector encoding vascular endothelial growth factor gene, in patients with critical limb ischemia due to poor peripheral vascularization.

f. Nervous system: *Parkinsons disease with delivery of genes involved in dopamine synthesis.*

- i. Delivery of neurotrophic factors to the CNS for the treatment of lateral sclerosis and for promoting recovery after spinal cord injury.

g. Infectious diseases: *Use of ribozymes to block HIV infection.*

- i. Vaccination with specific antigens.
- ii. Manipulation of immune system to enhance clearance of pathogens.

h. Cancers: *Melanoma*

- i. Delivery of genes to tumor cells, which convert a prodrug into a cytotoxic compound.
- ii. Delivery of gene products that interfere with tumor angiogenesis.
- iii. Lytic viral vectors that will selectively replicate and kill malignant cell are being developed.



S E C T I O N

2A

Autonomic Nervous System

Introduction to Autonomic Pharmacology

The nervous system is divided into:

- **Central** (includes brain and spinal cord)
- **Peripheral Nervous System**, which is again subdivided into:
 - Somatic Nervous Systems
 - Autonomic Nervous System

SOMATIC NERVOUS SYSTEM

The somatic nervous system innervates and controls the motor function of the body. It supplied to skeletal muscles. The nerve fibers are myelinated, there is no peripheral plexus formation. The neurotransmitter released at periphery is **Acetyl choline**. If we cut the nerve, there occur paralysis and atrophy in supplied muscles.

AUTONOMIC NERVOUS SYSTEM

- The autonomic nervous system (ANS) is **not under voluntary control** and therefore was so named by Langley (*Autos*=self, *nomos*=governing—in Greek).
- The ANS innervates and supplied to all the viscera, i.e. the heart, the smooth muscles, the glands and controls the functions of these organs.
- Like somatic nervous system ANS also consists of:
 - **Autonomic afferents:** Which carrying visceral pain, cardiovascular and respiratory reflexes to the central connections via dorsal root ganglion of spinal nerve and sensory ganglion of cranial nerve.
 - **Autonomic central:** The highest centres for autonomic nervous system are present in the hypothalamus, medulla and spinal cord. *Hypothalamus* coordinates the autonomic activity.
 - The postero-lateral nuclei regulate sympathetic activity while.
 - Anterio-medial nuclei regulate parasympathetic activity.

- **Autonomic efferent:** The ANS efferent consists of two major divisions—the **sympathetic** and the **parasympathetic**.

- Most of the viscera have both sympathetic and parasympathetic innervations.
- The two divisions, i.e. **sympathetic and parasympathetic** have opposing effects and normally their effects are in a state of equilibrium.
- The prime function of parasympathetic system is mainly to participate in tissue building reactions, i.e. it control the basal functions of the body like heart rate (72/min) and respiratory rate (14/min). While that of the sympathetic system is to help the person to adjust stressful situation and prepare the body for **(FFF) fight, fright and flight reactions (responses)**.
- Man can still survive without sympathetic system but not without parasympathetic.

Autonomic Innervations

- The autonomic afferents are carried in visceral nerves through nonmyelinated fibres. For example, the parasympathetic afferents are carried by the 9th and 10th cranial nerves.
- The autonomic efferent innervations consists of:
 1. A myelinated preganglionic fibre which synapses with
 2. A nonmyelinated postganglionic fibre. The postganglionic fibre in turn forms a junction with the receptors of the organs supplied by it.
- The junction between the pre-and postganglionic fibers is called a *ganglion*.
- The junction between the postganglionic fibers and the receptors is the *neuroeffector junction*, i.e. **neuromuscular junction**.
- The traveling of an impulse along the nerve fiber is known as *conduction* of action potential, while its passage across a synapse is known as *transmission* (neurotransmission).

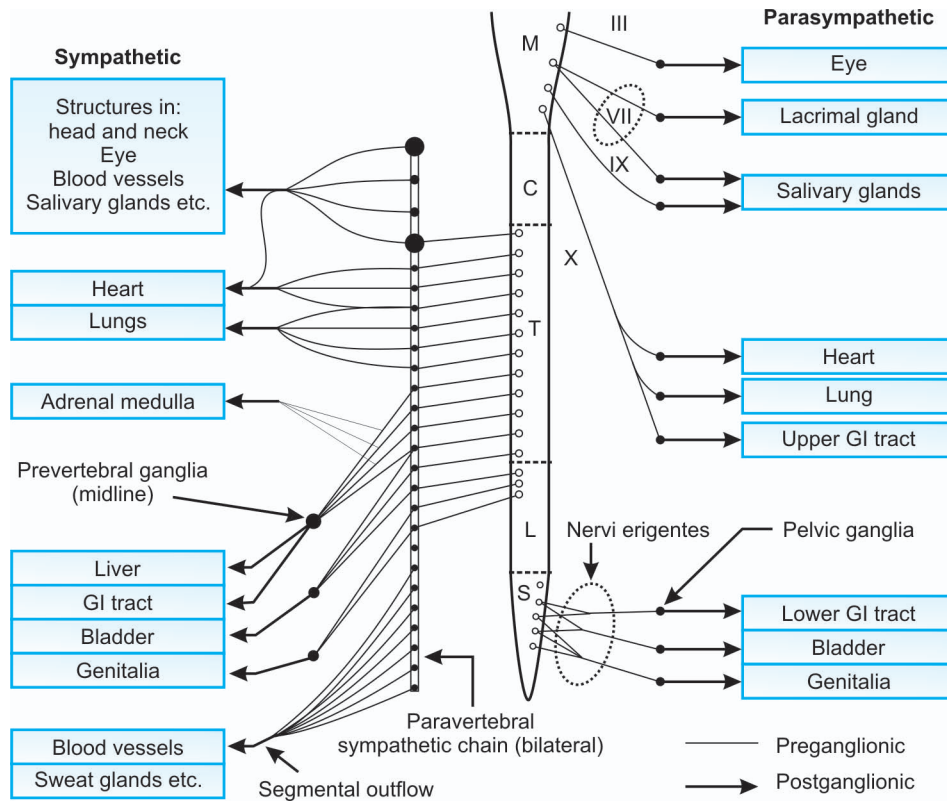


Fig. 2A.1.1: The autonomic nervous system. M = Medullary, C = Cervical, T = Thoracic, L = Lumbar, S = Sacral

The autonomic efferent is divided into sympathetic and parasympathetic divisions (Fig. 2A.1.1).

- **The parasympathetic efferents** are carried through the craniosacral (3, 7, 9 and 10th, $S_2 - S_4$) outflow. Its distribution is limited to head, neck and trunk only. The ganglia is located on or close to the organ while the neurotransmitter released is *Acetyl choline*, which is rapidly hydrolyzed locally.
- **The sympathetic efferents** extend from 1st thoracic to 2nd or 3rd lumbar segments ($T_1 - L_3$) of the spinal cord. The sympathetic ganglia are found at 3 sites: paravertebral, prevertebral and terminal. Postganglionic fibers arising from sympathetic ganglia innervate the head, neck and viscera of the thorax and abdomen. The major neurotransmitter is *Nor-adrenaline* while minor one is *Acetyl choline*.
- **Adrenal medulla** is also considered as sympathetic ganglia and differs from other sympathetic ganglia in that the principal catecholamine that is released is adrenaline.

SYNAPSE

It is a junction between two neurons where one neuron conducts the impulse in chemical form to the other, so that the impulse is transmitted from one neuron to the other.

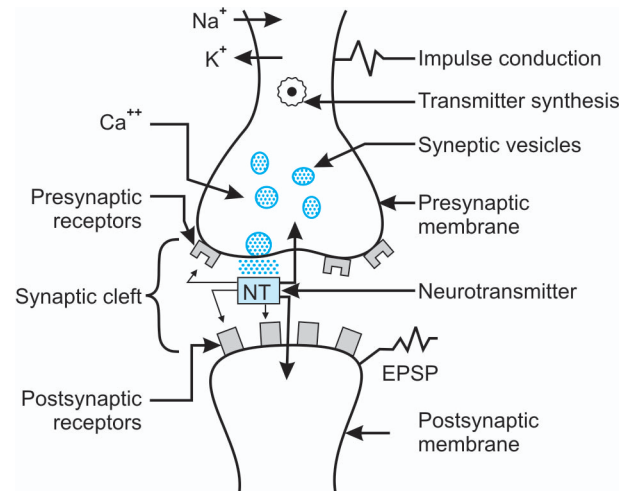


Fig. 2A.1.2: Neurohumoral transmission at synapse

NEUROHUMORAL TRANSMISSION

Neurohumoral transmission means nerves transmit their message across synapse (junction between two neurons) (Fig. 2A.1.2) and neuro-effector junction (junction between

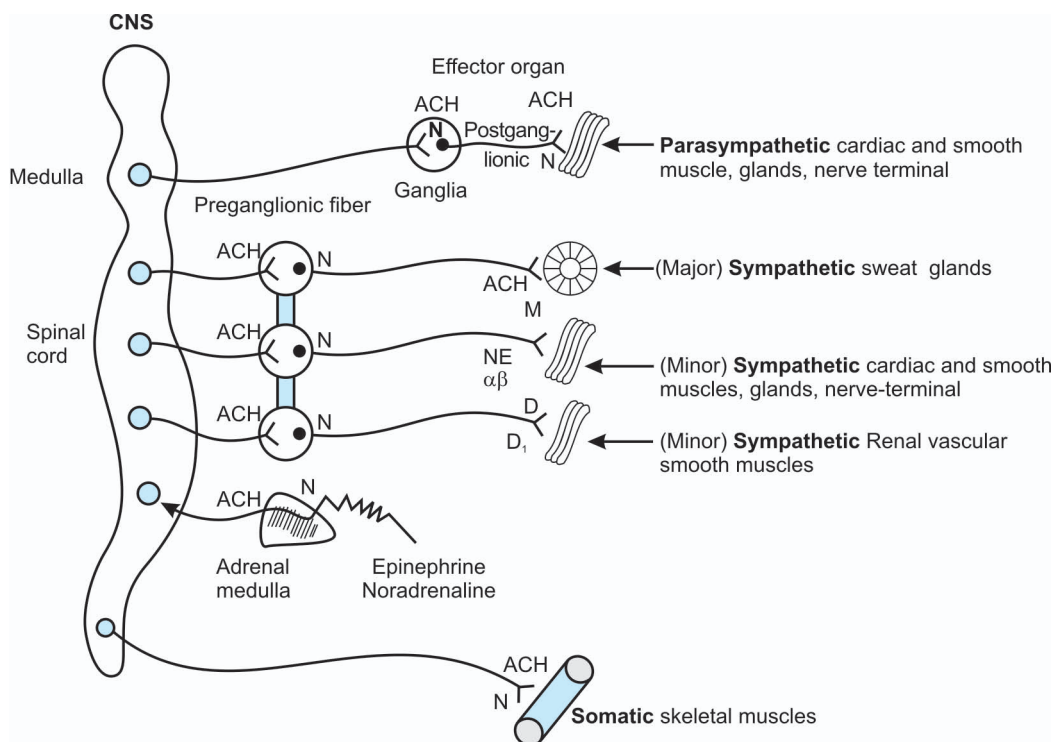


Fig. 2A.1.3: General outlay of autonomic nervous system

N = Nicotinic receptors, M = Muscarinic receptors, α , β = Adrenergic receptors, ACh = Acetylcholine, NE = Nor-epinephrine, D = Dopamine

nerve and organ) by the release of chemical (humoral) messenger. The steps in neurohumoral transmission are:

- **Impulse conduction:** Generation and propagation of action potential in axon.
- **Transmitter release:** Release of specific neurotransmitter from the terminal button on approach of action potential.
- **Transmitter action on postjunctional membrane:** The released neurotransmitter binds with the postjunctional receptors and produces: EPSP (Excitatory post synaptic potential) or IPSP (Inhibitory post synaptic potential).
- **Postjunctional activity:** EPSP generates a propagated postjunctional AP while IPSP stabilizes the postjunctional membrane.
- **Termination of transmitter action:** The neurotransmitter action gets terminated by immediate hydrolysis of transmitter or uptake of transmitter by surrounding tissue or nerve tissue.

Neurotransmitters of the autonomic nervous system (ANS): For the transmission of an impulse across a

synapse, a neurohumoral transmitter substance is released into the synaptic cleft. In the ANS:

- The principal transmitters are acetylcholine and noradrenaline.
- Preganglionic neurons are cholinergic, ganglionic transmission occurs via nicotinic ACh receptors (though excitatory muscarinic ACh receptors are also present on postganglionic cells). See Fig. 2A.1.3.
- Postganglionic parasympathetic neurons are cholinergic, acting on muscarinic receptors in target organs.
- Postganglionic sympathetic neurons are mainly noradrenergic, though a few are cholinergic (e.g. sweat glands).
- Transmitters other than noradrenaline and acetylcholine (NANC transmitters) are also used extensively in the autonomic nervous system. The main ones are nitric oxide and VIP (parasympathetic), ATP and NPY (sympathetic). Others, such as 5-HT, GABA and dopamine, also play a role (Fig. 2A.1.4).
- Co-transmission is a general phenomenon.

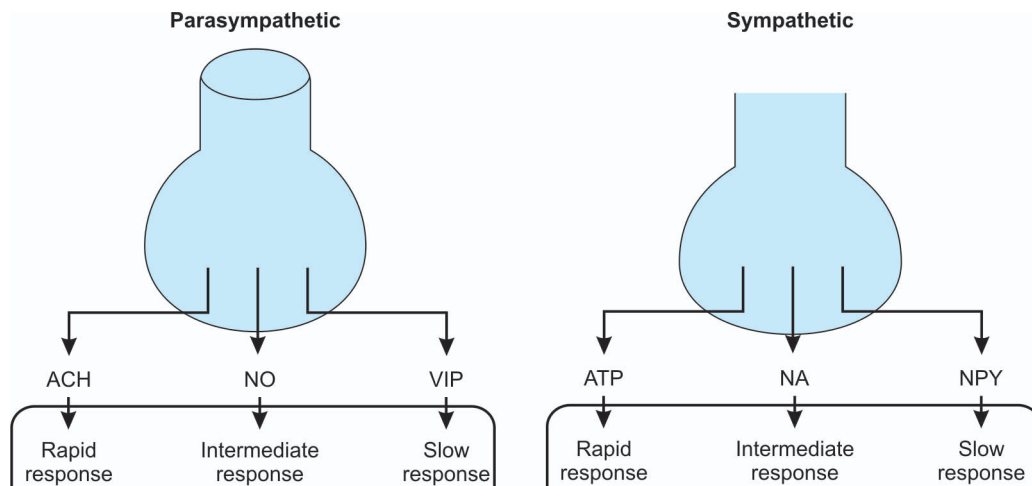


Fig. 2A.1.4: Co-transmission at parasympathetic and sympathetic neurons

ACh = Acetylcholine

NO = Nitric oxide

VIP = Vasoactive intestinal peptide

ATP = Adenosine triphosphate

NA = Noradrenaline

NPY = Neuropeptide-Y

Adrenergic System

ADRENERGIC SYSTEM

This system is also called as **Sympathetic System**. When people feel threatened, they have a natural and positive tendency to defend and protect themselves. This system works only during emergency conditions which are also known as FFF (**F₃**) conditions. The prime function of this system is to help the human beings to adjust to stress and prepare the body for fight, fright or flight reactions, when exposed to stress.

- On stimulation of this system the heart rate and stroke volume increase with the resultant increase in CO.
- The blood is shifted from the skin, gut, kidney and glands to the heart, skeletal muscles, brain and lungs, as these organs need more blood during stress.
- Pupils and bronchi are dilated and sweating is increased.
- Blood glucose increases by glycogenolysis as there is more need of energy during emergency.

Distribution of the Sympathetic System

- The sympathetic division consists of the thoracolumbar outflow extending from 1st thoracic to 2nd or 3rd lumbar segment.
- The sympathetic ganglia are paravertebral, prevertebral and terminal ganglia, i.e. adrenal medulla.
- *Location of preganglionic neurons:* In the sympathetic (thoracolumbar) nervous system, the neurons are located in lumbar and thoracic portions of the spinal cord.
- *Location of ganglia:* In the sympathetic nervous system, the ganglia are close to the spinal cord, so that the preganglionic axons are short and the postganglionic axons are long.

Neurotransmitters of the Sympathetic System

These are:

1. Noradrenaline (NA, norepinephrine) and
2. Dopamine (DA).

3. Adrenaline (epinephrine) is the major hormone secreted by the adrenal medulla. While in CNS it is also a major neurotransmitter at various sites, shown in Figure 2A.1.3 of previous chapter.

Noradrenergic Transmission

Transmitter synthesis: The 3 catecholamines – NA, adrenaline and DA are synthesized from the amino acid tyrosine. See Figure 2A.2.1 and 2A.2.2.

- L-tyrosine is converted to DOPA by *tyrosine hydroxylase* (rate-limiting step). *Tyrosine hydroxylase* is found only in catecholaminergic neurons.
- DOPA is converted to dopamine by *dopa decarboxylase*.
- Dopamine is converted to NA by *dopamine β -hydroxylase (DBH)*, located in synaptic vesicles.
- In the adrenal medulla, NA is converted to adrenaline by *phenylethanolamine N-methyl-transferase*.

Transmitter storage: NA is stored in high concentration in synaptic vesicles, together with ATP, chromogranin and DBH, all of which are released by exocytosis. Transport of NA into vesicles occurs by a reserpine-sensitive carrier, protein. NA content of cytosole is normally low, due to monoamine oxidase in nerve terminals (Fig. 2A.2.1).

Transmitter release: NA release occurs normally by Ca^{2+} mediated exocytosis from vesicles on the terminal network. Nonexocytotic release occurs in response to indirectly acting sympathomimetic drugs (e.g. amphetamine) which displace NA from vesicles. NA escapes via 'uptake 1' site (reverse transport) (Fig. 2A.2.1 and 2A.2.3).

Transmitter action: Its action is terminated mainly by reuptake of NA into nerve terminals. This uptake (uptake 1) is blocked by tricyclic antidepressant drugs.

Co-transmission: Occurs at many noradrenergic nerve terminals, ATP and neuropeptide Y being frequently co-released

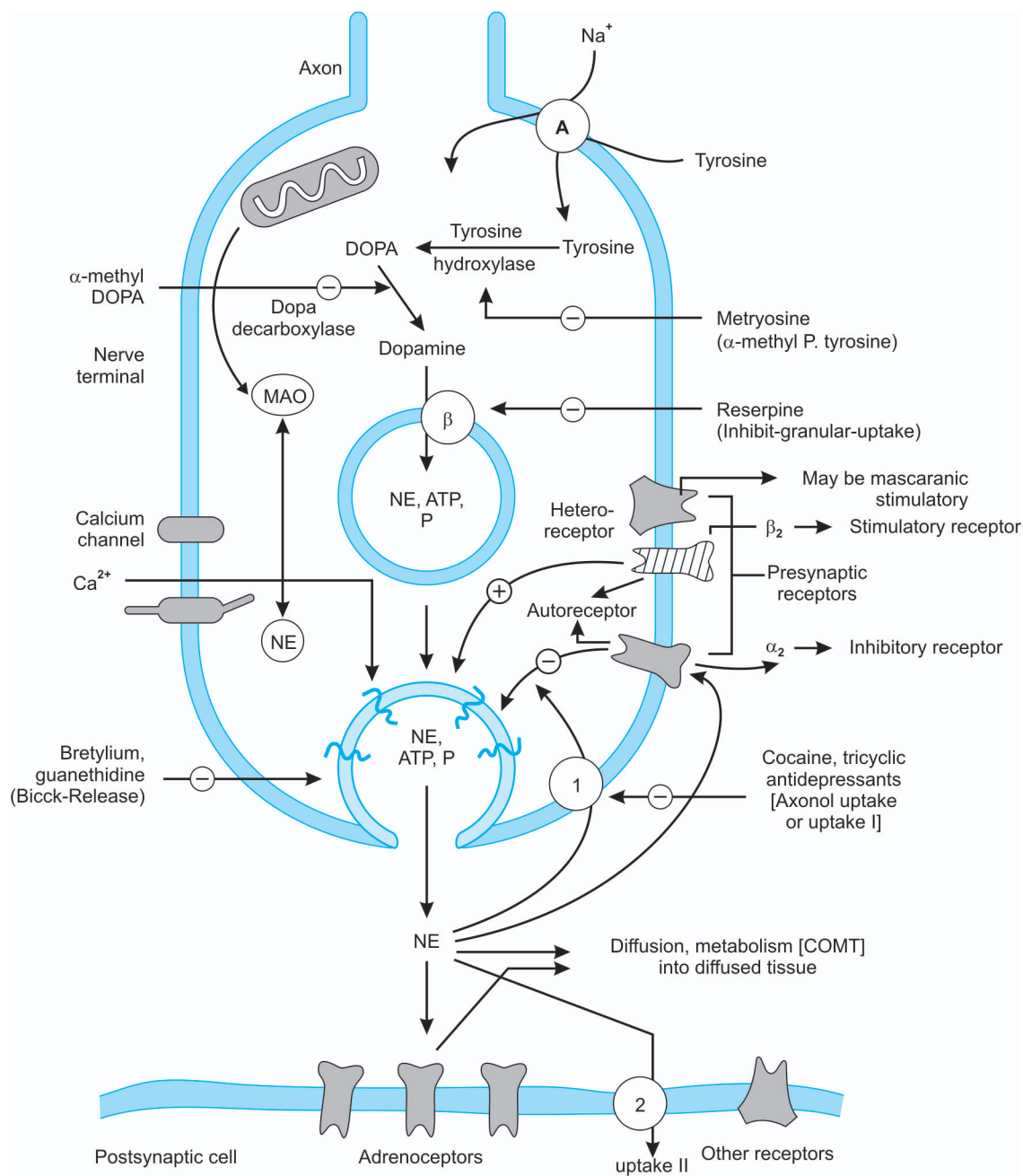


Fig. 2A.2.1: Noradrenergic transmission at synapse of adrenergic nerve with drugs affecting it

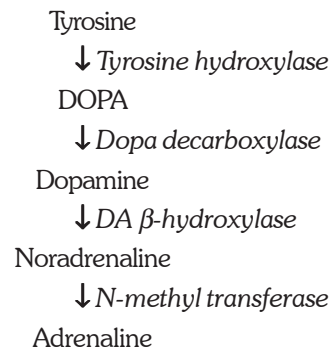


Fig. 2A.2.2: Biosynthesis of catecholamines

with NA. ATP mediates the early phase of smooth muscle contraction in response to sympathetic nerve activity. Figure 2A.1.4 of previous chapter.

- The sympathetic postganglionic nerve fibres that synthesize, store and release NA are called **adrenergic fibers**. See Figure 2A.2.2 and Table 2A.2.1.
- Large portion (nearly 80%) of NA is taken back into the nerve terminals by an energy dependant active transport process termed **uptake 1**, which is responsible for termination of action of NA.
- Of this, a fraction is metabolised by MAO and the remaining NA is then transferred to the storage vesicles. Some part of NA released into the synaptic cleft penetrates into the effectors cells and is known as **uptake 2** shown in figure 2A.2.1.

Adrenergic receptors: Adrenergic receptors are classified into alfa and beta subtypes, based originally on order of potency among agonists, later on selective antagonists.

α -Adrenergic receptors:

- **Agonists**, in decreasing order of potency, are Epinephrine > Norepinephrine > Isoproterenol.
- **Antagonists** are phentolamine and phenoxybenzamine.

Some α -adrenergic receptors precede the synapse between nerve terminal and effector organ; others are postsynaptic.

1. **α_1 -Adrenergic receptors:** They are postsynaptic receptors. They are found in the blood vessels, in the radial muscle of the eye, in the gastrointestinal tract, and in the splenic capsule.
2. **α_2 -Adrenergic receptors:** They are presynaptic or postsynaptic; all seem to serve an inhibitory function. Isoproterenol is ineffective on α_2 -receptors.

- a. Presynaptic α_2 -receptors are found at adrenergic and cholinergic nerve terminals. Presynaptic α_2 -receptors, when activated, inhibit the further release of neurotransmitter.
- b. Postsynaptic α_2 -receptors are found in blood vessels and in the CNS.

β -Adrenergic receptors:

- **Agonists for β -receptor:** They are isoproterenol, epinephrine, and norepinephrine.
 - Propranolol is an **antagonist**. The β -receptors are also subdivided on the basis of their relative response to agonists and antagonists.
- 1. **β_1 -Adrenergic receptors:** They are found predominantly on cells in the heart and JG Apparatus. The relative potency of agonists is isoproterenol > epinephrine and norepinephrine.
- 2. **β_2 -Adrenergic receptors:** They are found at other sites, most importantly, on bronchial and vascular smooth muscle. The relative potency of agonists is isoproterenol > epinephrine > norepinephrine.

Mechanism of Action

- There are two main α -adrenoceptor subtypes (α_1 , α_2) and three β -adrenoceptor subtypes (β_1 , β_2 , β_3). Cloning studies show that all belong to the superfamily of G-protein-coupled receptors.
- **Second messengers:** α_1 -receptors activate phospholipase C, thus producing IP_3 and DAG as second messengers; α_2 -receptors inhibit adenylate cyclase, and thus decrease cAMP formation; all types of β -receptor stimulate adenylate cyclase.
- The main effects of **receptor activation** are:
 - α_1 -receptors-vasoconstriction, relaxation of gastrointestinal smooth muscles, salivary secretion and hepatic glycogenolysis.
 - α_2 -receptors-inhibition of transmitter release (including NA and ACh release from autonomic nerves), platelet aggregation, contraction of vascular smooth muscle, inhibition of insulin release.
 - β_1 -receptors-increase in cardiac rate and force of contraction.
 - β_2 -receptors-bronchodilatation, vasodilatation, relaxation of visceral smooth muscles, hepatic glycogenolysis and muscle tremor.
 - β_3 -receptors, lipolysis.

Table 2A.2.1: Sites of action of drugs affecting the sympathetic nervous system as shown in Fig. 2A.2.3

Site	Process	Inhibitor
1	Tyrosine uptake	None
2	Tyrosine hydroxylase (TH)	α -Methyl-p-tyrosine, dopamine (DA), norepinephrine (NE)
3	Dopa decarboxylase(DD)	α -Methyldopa
4	Movement of DA into vesicles	Reserpine
4A	Movement of NE back into vesicles	
5	Dopamine β -hydroxylase (DBH)	Disulfiram
6	Depolarization of adrenergic terminals	Bretylum, guanethidine
7	Exocytotic release of NE	See site 6
8	Release by indirect-acting sympathomimetics	Cocaine (block uptake), reserpine (eliminates stores)
9	α_1 -Adrenergic receptors (postsynaptic)	Phentolamine, tolazoline, phenoxybenzamine, ergotamine, prazosin
10	β_1 -Adrenergic receptors	Atenalol, metoprolol
11	β_2 -Adrenergic receptors	Propranolol (also β_1)
12	α_2 -Adrenergic receptors (presynaptic)	See site 9 (not prazosin)
13	Norepinephrine uptake (U-1)	Cocaine, imipramine, ouabain, bretylum, guanethidine, phenoxybenzamine
14	Extraneuronal uptake (U-2)	Phenoxybenzamine, corticosterone, normetanephrine
15	Catechol O-methyltransferase (COMT)	Pyrogallol, entacapone, tolcapone.
16	Monoamine oxidase (MAO)	Phenelzine (a hydrazine), tranylcypromine (derivative of amphetamine)

Drug Effects on Neurohumoral Transmission

- Drugs can affect neurohumoral transmission at various steps. They can affect the following:
 - Synthesis, storage, or release of a neurotransmitter
 - Interaction between transmitter and receptor
 - Enzymatic destruction of a neurotransmitter
 - Transport of a transmitter into cells
 - Recovery of a cell membrane after the transmitter-receptor interaction
- Figure Illustrated and Table show the mechanisms and sites of drug effects on the sympathetic nervous system (Fig. 2A.2.3).

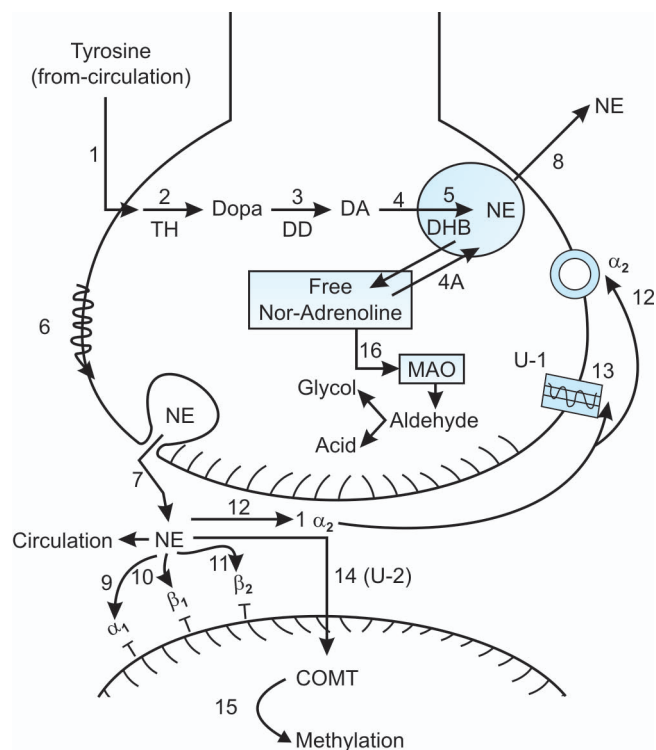


Fig. 2A.2.3: Synthesis and release of Nor-adrenaline with encoded site of action of drugs affecting the sympathetic nervous system.

DD = Dopa decarboxylase
 DA = Dopamine
 DBH = Dopamine β -hydroxylase
 NE = Nor-epinephrine

Adrenergic Drugs (Sympathomimetics)

Definition: Adrenergic or Sympathomimetic drugs are the agents which mimic (act like) that of adrenaline, or of sympathetic stimulation.

They can be classified in various ways (Tables 2A.3.1 and 2A.3.2):

Classification based on the mode of action:

- 1. Directly acting Sympathomimetics:** By interacting with adrenergic receptors: *NA, Isoprenaline, Dopamine, Adrenaline.*
- 2. Indirectly acting Sympathomimetics:** By releasing NA from nerve terminals : *Tyramine*
- 3. Mixed acting Sympathomimetics:** They act directly as well as indirectly : *Amphetamine, ephedrine.*

Chemical classification: Based on presence/absence of catechol ring (nucleus).

- 1. Catecholamines:** Noradrenaline(NA), Adrenaline, Dopamine(DA),
- 2. Non-catecholamines:** Ephedrine, Amphetamine

Table 2A.3.1: Classification based on therapeutic or clinical use

- 1. Nasal decongestants:** *Ephedrine, Pseudoephedrine, Phenylpropanolamine, Phenylephrine, Oxymetazoline, Xylometazoline*
- 2. Bronchodilators:** *Adrenaline, Isoprenaline, Salbutamol, Terbutaline, Salmeterol*
- 3. Cardiac stimulants:** *Adrenaline, Dopamine, Dobutamine, Isoprenaline, Ephedrine*
- 4. Pressors:** *Noradrenaline, Dopamine, Methoxamine, Metaraminol*
- 5. Uterine relaxants:** *Salbutamol, Terbutaline, Isoxuprine, Ritodrine*
- 6. Appetite suppressants:** *Fenfluramine, Dexfenfluramine (anorectics)*
- 7. CNS stimulants:** *Amphetamine, Ephedrine*

Table 2A.3.2: Adrenoceptor agonists

- Selective drugs exist for the main adrenoceptor subtypes, α_1 , α_2 , β_1 , β_2 . NA itself shows some selectivity for α -over β -adrenoceptors; adrenaline shows little selectivity.
- Selective α_1 -agonists include phenylephrine, oxymetazoline.
- Selective α_2 -agonists include clonidine, α -methylnoradrenaline. They cause a fall in blood pressure, partly by inhibition of NA release, and partly by a central action. Methylnoradrenaline is formed as a false transmitter from methyl dopa, developed as a hypotensive drug (now largely obsolete).
- Selective β_1 -agonists include dobutamine. Increased cardiac contractility may be useful clinically, but all β_1 -agonists can cause cardiac dysrhythmias.
- Selective β_2 -agonists include salbutamol, terbutaline and salmeterol, used mainly for their bronchodilator action in asthma.
- Selective β_3 -agonists are being developed for the control of obesity.

Pharmacokinetics

- Absorption is poor with oral administration because the drugs are rapidly conjugated and oxidized.
- Absorption is slow with subcutaneous administration because the drugs cause local vasoconstriction.
- Nebulized and inhaled solutions are usually used for their actions on the respiratory tract.
- The drugs can be given intravenously, but this route must be used with caution so that the heart does not fibrillate.
- Catecholamines are rapidly metabolized in the gut and the liver therefore they are not given orally.

ACTIONS (Table 2A.3.3)**Cardiovascular System**

Heart: Acting through β_1 receptors, adrenaline

- Increases the heart rate,
- Increases force of contraction,
- Increases conduction velocity.

It is a powerful cardiac stimulant. There occurs increase in cardiac output and work Load and therefore the resultant O_2 consumption of the heart is also increased.

Blood vessels

- Vasoconstriction in the blood vessels of mucous membrane and skin (α_1) and
- Vasodilatation in the blood vessels of that of skeletal muscles (β_2).
- Since adrenaline causes mucosal vasoconstriction, it is useful in dental practice to arrest post-extraction bleeding and to prolong duration of action of local anesthetics.

Blood pressure

- **Adrenaline** ($\alpha_1, \alpha_2, \beta_1$ & β_2) in moderate doses (IV) produces a rapid increase followed by a fall in BP: a *biphasic response*. The rise in pressure is due to α_1 mediated vasoconstriction. Action on β receptors is more persistent and as the action on alpha receptors diminishes, the action on β receptors gets unmasked resulting in $\downarrow$ BP (Fig. 2A.3.1).

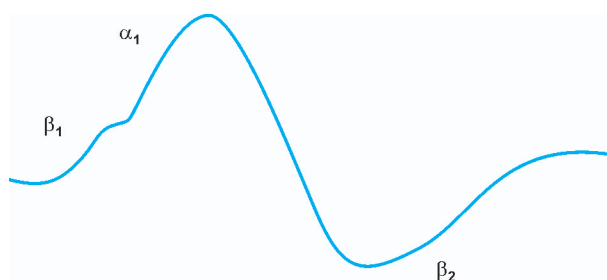


Fig. 2A.3.1: A biphasic response of Adrenaline

1. Slow IV. injection of adrenalin: rise in systolic BP (β_1 and α_1), but fall in diastolic BP (β_2). Both mean blood pressure and pulse pressure rises.
2. Rapid IV. injection of adrenaline: rise in both systolic and diastolic BP.
 - Adrenaline causes renal vasoconstriction resulting in fall in renal blood flow; it also causes pulmonary and mesenteric vasoconstriction
 - Cerebral and coronary blood flow is enhanced.
- **Sir Henry Dale** demonstrated that when α receptors are blocked (with alpha blockers—ergot alkaloids), adrenaline produces only a fall in BP and this is named

after him as **Dale's vasomotor reversal** (or Dale's phenomenon).

- **Noradrenalin** ($\alpha_1, \alpha_2, \beta_1$) and no β_2 :
 - It is predominately an alpha agonist and brings about a rise in BP.
 - There occurs rise in systolic, diastolic as well as mean blood pressure.
- **Isoprenaline** (β_1 and β_2), no α activity.
 - There occurs rise in systolic BP, but fall in diastolic BP, Mean BP also fall.

$$\text{Mean BP} = \text{Diastolic Pressure} + \frac{\text{Pulse pressure}}{3}$$

$$\text{Pulse Pressure} = \left[\text{Systolic Pressure} \right] - \left[\text{Diastolic Pressure} \right]$$

Respiration

- **Bronchi:** Adrenaline and isoprenaline are powerful bronchodilator and a weak respiratory stimulant.
- Pulmonary vasoconstriction relieves bronchial congestion.
- Noradrenaline has no bronchodilator effect due to absence of β_2 receptor.
- All these effects results in increase in vital capacity.

Eye: Adrenaline causes **mydriasis** due to contraction of the radial muscles of the iris (α_1); it also reduces intraocular tension (fall in IOT), specially in wide angle glaucoma.

GIT

- Gut smooth muscle is **relaxed**: but it is a weak and transient action.
- Peristalsis also reduces. (decreased)
- Sphincters: (pyloric and anal) constricted.

Metabolic effects

- Adrenaline increases the blood sugar level by enhancing hepatic **glycogenolysis**.
- It also inhibits insulin release (α_2) Enhancing breakdown of triglycerides in the adipose tissue, more free fatty acids are made available in the plasma by action on β_3 receptors in adipocytes.
- $\uparrow$ Glucagone secretion (β_2)

Splenic capsule: Contracts (α_1); resulting in the release of RBCs into the circulation.

Bladder

- Detrusor is relaxed (β_2 receptors)
- While trigone (sphincter) (" α_1 ") is contracted thereby increasing the holding capacity of the bladder and inhibition of sphinctor.

Uterus: In general relaxation of uterus due to (β_2) action

	Nonpregnant	Pregnant
<i>Rat</i>	Relaxed	Relaxed
<i>Rabbi</i>	Contracted	Contracted
<i>Cat</i>	Relaxed	Contracted
<i>Human</i>	Contracted	Relaxed

Skeletal muscles

- Catecholamines facilitate neuromuscular transmission by action on both α and β receptors—they enhance the amount of ACh released.
- Pilomotor muscles of the hair follicle contract.

Table 2A.3.3: Direct effects of autonomic nerve activity and autonomic drugs on some organ systems

Organ	Effect of			
	Sympathetic		Parasympathetic	
	Action	Receptor	Action	Receptor
Eye				
Iris				
Radial muscle	Contracts	α_1		
Circular muscle			Contracts	M_3
Ciliary muscle	[Relaxes]	β	Contracts	M_3
Heart				
Sinoatrial node	Accelerates	β_1	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1		
Contractility	Increases	β_1	Decreases (atria)	M_2
Vascular smooth muscle				
Skin, splanchnic vessels	Contracts	α		
Skeletal muscle vessels	Relaxes	β_2		
	[Contracts]	α		
	Relaxes	M		
Endothelium			Releases EDRF	M_3
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M_3
Gastrointestinal tract				
Smooth muscle				
Walls	Relaxes	α_2, β_2	Contracts	M_3
Sphincters	Contracts	α_1	Relaxes	M_3
Secretion			Increases	M_3
Myenteric plexus	Inhibits	α	Activates	M_1
Genitourinary smooth muscle				
Bladder wall sphincter	Relaxes	β_2	Contracts	M_3
Sphincter	Contracts	α_1	Relaxes	M_3
Uterus, pregnant	Relaxes	β_2		
	Contracts	α	Contracts	M_3
Penis, seminal vesicles	Ejaculation	α	Erection	M
Skin				
Pilomotor smooth muscle	Contracts	α		
Sweat glands				
Thermoregulatory	Increases	M		
Apocrine (stress)	Increases	α		
Metabolic functions				
Liver	Gluconeogenesis	α/β_2		
Liver	Glycogenolysis	α/β_2		
Fat cells	Lipolysis	β_3		
Kidney	Renin release	β_1		
Autonomic nerve endings				
Sympathetic				
Parasympathetic	Decreases ACh release	α	Decreases NE release	M

[Specific receptors types α = alpha, β = beta, M = Muscarinic] [EDRF = Endothelial Derived Relaxing Factors]

CNS

- IV or SC injections have no CNS effects due to poor penetration, but in higher dose it causes convulsion and restlessness.
- Intracranial injection causes excitation followed by depression, fall in BP and bradycardia.

Termination of action

- Transport, or uptake into the cells, is an important mechanism for terminating the action of many neurotransmitters. There are two active amine transport systems:
 - A system in the plasma membrane transports amines from the extracellular fluid to the cytosol.
 - A system in the secretory granular membrane transports amines into granules.
- The liver is important in the degradation of adrenaline (epinephrine) and nor-adrenaline (norepinephrine). The majority of the dose is metabolized by catechol O-methyltransferase (COMT) and monoamine oxidase (MAO), and the metabolites are excreted in the urine (see Fig. 2A.3.2).

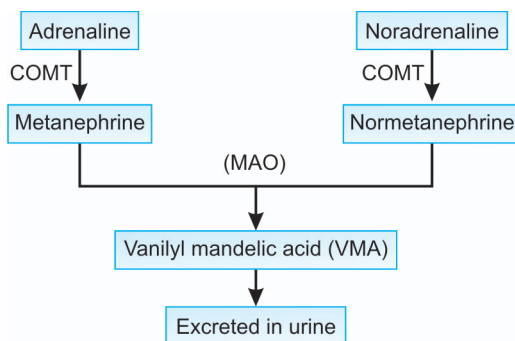


Fig. 2A.3.2: Termination of action of catecholamines

Therapeutic uses of adrenaline**Cardiovascular system**

- Cardiac arrest: **Adrenaline** is the drug of choice (0.3-0.5 ml of 1:1000 solution). It promptly reverses hypotension, laryngeal edema and bronchospasm and is life saving in **anaphylactic shock**. IM route or intravenous, is preferred as absorption by SC route is not reliable in shock.
- Cardiogenic shock and CCF: **dobutamine** (β_1 -agonist) by intravenous infusion for its positive inotropic effect; low-dose **dopamine** to increase renal perfusion (via dopamine receptors in renal vasculature) and maintain glomerular filtration.
- Cardiac arrest or Heart block: Symptomatic heart block is treated by electrical pacing: β -agonists (**isoprenaline, dobutamine**) can be used temporarily. Sudden cardiac arrest due to drowning, electrocution, etc. are treated with intracardiac adrenaline (into 4th or 5th

intercostal space, 2-3 inches from the sternum); before injecting, ensure that the tip of the needle is in the heart.

- Stokes Adams syndrome and
- Partial or complete A/V block.

Anaphylactic Reactions

- Acute anaphylactic (or Type I hypersensitivity) reactions and sometimes life-threatening immunological reactions are usually caused by bee stings or by hypersensitivity reactions due to drugs (especially **penicillin**).
- The main clinical manifestations are gross swelling of the skin and mucous membranes, which can obstruct breathing, and cardiovascular collapse due to vasodilatation.
- **Adrenaline** is the first-line treatment, usually injected intramuscularly, intravenous infusion requires close monitoring, usually in an intensive care unit.

Control of hemorrhage: Adrenaline in 1:10,000 to 1:20,000 concentration is used as a topical hemostatic to control bleeding. Bleeding stops due to vasoconstriction. Adrenaline packs are used for bleeding after tooth extraction and in epistaxis.

Respiratory System

- **Acute bronchial asthma:** Adrenergic drugs specially selective β_2 receptor agonists like (salbutamol, terbutaline, salmeterol, bronchodilatation on inhalation. [For Detail: See Chapter Bronchial asthma]
- Nasal decongestion: drops containing **oxymetazoline** or **ephedrine** for short-term use.

Glaucoma: Adrenaline reduces Intraocular Pressure and can be used in glaucoma.

Miscellaneous Indications**With local anesthetics**

- Prolongation of local anesthetic action: vasoconstrictor agents such as **adrenaline** can be injected with the local anesthetic solution. Injected with LA, adrenaline produces vasoconstriction and reduces the rate of absorption of LA. By this it prolongs the action and reduces systemic toxicity of LA. 1:10,000 to 1:2,00,00 adrenaline is used. It must not be injected into fingers because of the risk of gangrene.
- Inhibition of premature labour (**salbutamol**).
- Miscellaneous indications for α_2 -agonists (e.g. **clonidine**) include hypertension, menopausal flushing, lowering of intraocular pressure and migraine prophylaxis.

Adverse Reaction

- Anxiety, palpitation, weakness, tremors, pallor, dizziness, restlessness and throbbing headache may follow adrenaline/NA administration.

- In patients with ischemic heart disease, both adrenaline and NA can precipitate anginal pain attack.
- Rapid IV injection can cause sudden sharp rise in BP which may precipitate arrhythmias, subarachnoid hemorrhage or hemiplegia.

Preparations (Adrenaline)

- Adrenaline 1:1000, 1:10,000 and 1:1,00,000 solutions are available for injection.
- Adrenaline is given SC/IM; intracardiac in emergencies.
- Adrenaline aerosol for inhalation and 2% ophthalmic solution are also available.

Noradrenaline: It can be used in shock to increase BP – but it is very rarely used. It is sometime used to treat septic shock. $\beta_1(+)$, $\beta_2(-)$

Isoprenaline (Isoproterenol, Isopropylarterenol)
It is a synthetic catecholamine (catechol ring). It has an N-alkyl substitution, which makes it act almost entirely on β -receptors and have little effect on α -receptors.

Pharmacokinetics

- Absorption of orally administered isoproterenol is unreliable.
- It has high first pass effect, therefore ineffective by oral route.
- It is readily absorbed when given parenterally or as an inhaled aerosol.
- It is principally metabolized by COMT; MAO plays a smaller role than in epinephrine or norepinephrine metabolism. Higher degradation occurs in GIT and liver.
- There is no neuronal uptake like adrenaline and noradrenalin.

Pharmacological effects

- Intravenous infusion produces a reduction of peripheral vascular resistance in skeletal muscles and in renal and mesenteric vascular beds.
- Diastolic blood pressure falls, but because there are increased venous return and positive inotropic and chronotropic effects, cardiac output is increased.
- Systolic blood pressure may increase, but mean pressure decreases.
- Renal blood flow decreases in normotensive individuals, but it increases in patients with non hemorrhagic shock.
- Relaxation of both bronchial and gastrointestinal smooth muscle occurs.
- A release of free fatty acids occurs; hyperglycemia is less than with epinephrine.
- Pancreatic islet cells are activated, stimulating insulin secretion.

Therapeutic use: Isoprenaline is used in heart block, and shock for its cardiac stimulant actions. It can be used in bronchial asthma.

Adverse effects

- Adverse effects of isoprenaline are similar to the adverse effects of epinephrine.
- These effects include palpitation, angina, headache and flushing, etc.
- Overdosage by inhalation can induce fatal ventricular arrhythmias.
- Tolerance to the desired effects occurs with overuse in the asthmatic.

Dopamine

Chemistry

- It is a catecholamine, precursor of norepinephrine. Dopamine is an intermediate in the synthesis. It acts on dopaminergic and adrenergic receptors.
- It is a central neurotransmitter.

Pharmacokinetics: Dopamine resembles epinephrine and norepinephrine in its Pharmacokinetics.

Receptors: Central dopamine receptors (D_1 , D_2 , D_3 , D_4 and D_5)

1. The D_1 receptor site is excitatory and directly activates the adenylate cyclase system.
 2. The D_2 receptor site is inhibitory in some brain tissues and uses cAMP as its intracellular messenger. Pituitary-related side effects of neuroleptics are thought to be mediated through D_2 receptors in the pituitary.
 3. The D_3 receptor is localized in the limbic system and is not found in the pituitary. It is principally associated with emotional and cognitive behavior.
- For details, see the chapter Neurotransmitters in CNS.

Pharmacological effects

- **Low or intermediate doses (D_1 and D_2)** of dopamine reduce arterial resistance in the mesentery and kidney; this raises the glomerular filtration rate (GFR). The effect is mediated by a receptor for dopamine.
- **Moderate dose** causes cardiac stimulation through β_1 receptors; $\uparrow F_c$ and $\uparrow BP$ and (positive chronotropic and positive inotropic effects)
- Dopamine is an important neurotransmitter in the CNS. It is a direct agonist, acting on β_1 -receptors and releasing norepinephrine from nerve terminals. The results is a positive inotropic effect on the myocardium.
- **At higher doses**, it acts on α -receptors and causes vasoconstriction with a consequent reduction in renal function and (rise in Blood Pressure) $\uparrow BP$.

- Dopamine increases systolic pressure but has little effects on diastolic pressure.

Therapeutic uses

- DA is used in the treatment of shock—cardiogenic, hypovolemic and septic shock.
- It is specially useful when there is renal dysfunction and low cardiac output.

Adverse effects

- Overdosage results in excessive sympathomimetic activity.
- Nausea, vomiting, palpitation, angina, sudden (rise) in BP may occur, but these effects are short-lived because dopamine has rapid metabolism.

Dobutamine

- It is a congener of dopamine. It is a relatively selective β_1 agonist.
- It shows optical isomerism. Both $\pm$ isomers (mixture) act as an agonist for both beta-1 and beta 2 receptors.

Pharmacokinetics

- Dobutamine is not absorbed when given orally.
- It has a half-life of 2 minutes (short), when given by intravenous injection.

Pharmacological effects

- Although dobutamine resembles dopamine chemically, it is a direct β_1 -receptor agonist. It has a greater inotropic than chronotropic effect.
- Dobutamine does not act on dopaminergic receptors.

Therapeutic uses: Dobutamine is used to improve myocardial function in congestive heart failure, i.e. it **increases force of contraction of the heart** without a significant increase in the heart rate. Oxygen demands are less than with other sympathetic agonists.

Adverse effects

- Dobutamine increases atrioventricular conduction and must, therefore, be used with caution in atrial fibrillation.
- Other adverse effects are similar to those of other catecholamines.

Non-Catecholamines

- They are devoid of catechol nucleus, they act both by direct stimulation of adrenergic receptors and indirectly by releasing NA.
- In contrast to catecholamines, they are effective orally, relatively resistant to MAO and therefore are longer-acting; they cross the blood-brain barrier and have CNS effects.

Ephedrine: It is an alkaloid obtained from the plants of the genus *Ephedra*.

Pharmacokinetics

- Ephedrine is absorbed when taken orally.
- It is resistant to COMT and MAO, so that its action is prolonged.

Pharmacological effects

- Ephedrine is a mixed-acting sympathomimetic agent; that is, it has both direct and indirect actions.
 1. Its primary action is indirect. It causes the release of norepinephrine from storage in nerve terminals, apparently by competing with norepinephrine for transport into the granules.
 2. It also produces direct stimulation of adrenergic receptors.
- When administered intravenously, its action is similar to that of epinephrine. However,
 1. Its pressor response occurs more slowly and lasts 10 times longer as compared to epinephrine.
 2. Its potency is 1/250 that of epinephrine in producing an equivalent pressor response
- Ephedrine increases arterial pressure by causing peripheral vasoconstriction and cardiac stimulation.
- Its effects on the bronchi and other smooth muscle are qualitatively similar to those of epinephrine.
- It causes CNS stimulation, which can result in effects such as insomnia, nervousness, nausea, and agitation.
- **Tachyphylaxis** occurs with repeated administration.

Therapeutic uses

1. **Nasal decongestion:** Nasal drops of ephedrine are used. Pseudoephedrine: an isomer of ephedrine is used orally for decongestion.
2. **Mydriasis:** Ephedrine eye drops are used to produce mydriasis without cycloplegia.
3. **Hypotension:** For prevention and treatment of hypotension during spinal anesthesia—IM ephedrine is used.
4. **Bronchial asthma:** Ephedrine is useful in mild chronic bronchial asthma but again due to availability of better drug, it is not preferred.
5. **Nocturnal enuresis (Bed wetting):** Children may be treated with ephedrine as it increases the holding capacity of the bladder. *Drugs should be used only when non-pharmacological measures have failed.*
6. **Narcolepsy:** It is a condition with an irresistible desire and tendency to sleep. As ephedrine is a CNS stimulant, it is useful in the treatment of narcolepsy.
7. **Stokes Adam's syndrome:** It can be used as an alternative to isoprenaline.

Adverse effects

- These are similar to the adverse effects seen with epinephrine.
- In addition, CNS effects may occur.
- Ephedrine must be used with caution in patients with cardiovascular disease or hyperthyroidism because it is a powerful cardiac stimulator.

Amphetamine

- It is a non catecholamine.
- No effect of COMT, on it, therefore, it can be taken orally.
- It is a synthetic compound with actions similar to ephedrine, tolerance can occur on repeated use. It crosses BBB and therefore produces both CNS and peripheral action.

Mechanism of action

- It causes release of nor-adrenalin in CNS
- It causes release of dopamine and 5 HT in CNS (NT)
- It causes release of Nor-adrenaline in periphery.

Action of amphetamine

- Mood: produces depression
- Sleep: reduces sleep
- Hunger: reduces hunger and appetite
- In higher dose amphetamine causes release of Dopamine therefore produces schizophrenic like condition
- Amphetamine is a potent CNS stimulant; it crosses blood brain barrier produces increased mental and **physical activity, alertness, wakefulness, increased concentration and attention span elation, euphoria and increased capacity to work.**
- **It also increases initiative and self confidence, postpones fatigue and improves physical performance (temporarily) as seen in athletes.** All these properties make amphetamine drug of dependence and abuse (DOPING). Higher doses produce confusion, delirium and hallucinations. The effects may be reversed with over dosage.
- **Respiration:** Amphetamine stimulates respiration—*analeptic*.
- **Depression of appetite:** Acting on the feeding, center in the hypothalamus.
- **Amphetamine:** Also has weak anticonvulsant property.
- **Adverse effects:** include *restlessness, tremors, insomnia, palpitation, anxiety, confusion and hallucinations. Prolonged use may precipitate psychosis.*
- **High doses:** cause angina, delirium, arrhythmias, hypertension, acute psychosis, coma and death due to convulsions.
- **Dependence:** Amphetamine causes psychological dependence.

Uses

1. *Attention deficit hyperactivity disorder (ADHD)* in children it is characterized by decreased ability to concentrate and hold attention, aggressive behavior and hyperactivity.
2. *Narcolepsy:* Amphetamine is preferred over ephedrine.
3. *Epilepsy:* Amphetamine can be used as adjuvant and to counter the sedation due to antiepileptics.
4. *Obesity*
5. *Nocturnal enuresis and*
6. *Parkinsonism, etc.*

PRESSORS AGENTS. These are α_1 agonists and include:

Phenylephrine**Pharmacological effects**

- Phenylephrine is a direct-acting sympathomimetic agent. Its effects are similar to those of norepinephrine, but it is less potent and has a longer duration of action.
- Vasoconstriction, increased atrial pressure, and reflex bradycardia occur with parenteral administration.

Therapeutic uses: Phenylephrine is used

- As a nasal decongestant
- As a pressor agent
- To provide local vasoconstriction as:
 - A 10% ophthalmic solution
 - An adjunct for use with local anesthetics
- For relief of paroxysmal atrial tachycardia

Adverse effects

- Large doses cause cardiac irregularities.
- Ophthalmic solutions, and intranasal solutions, can be systemically absorbed. Their use in patients taking β -blockers increases the risk of cardiac irregularities, myocardial infarction, and intracranial hemorrhage.
- Rebound nasal congestion can occur with chronic use as a nasal decongestant.
- Phenylephrine, metaraminol, mephenteramine, and methoxamine, increases the BP by increasing total peripheral resistance (TPR) or cardiac output (CO) or both. They are given parenterally with constant monitoring of BP. Tachyphylaxis may develop.
- **Metaraminol** is an alpha stimulant and also acts indirectly by NA release. CO is increased. It is also a nasal decongestant.
- **Mephenteramine** acts on both α and β receptors to $\uparrow$ TPR, $\uparrow$ CO and thereby raises BP. It is orally effective. Pressor effect is accompanied by bradycardia.
- **Phenylephrine** is a selective α_1 stimulant; it is also a nasal decongestant. Reflex bradycardia is prominent. It produces mydriasis without cycloplegia.
- **Methoxamine** has actions similar to phenylephrine.

- Vasopressors are used to raise the BP in hypotension as seen in cardiogenic or neurogenic shock and during spinal anesthesia.

NASAL DECONGESTANTS are α_1 agonists which relieve congestion due to vasoconstriction.

They may be used:

1. *Orally* Ephedrine, Pseudoephedrine
 2. *Topically* Oxymetazoline, Xylometazoline, Naphazoline, Phenylephrine, Mephenteramine, Metaraminol
- Irritation and after congestion are disadvantages
 - On prolonged use intense vasoconstriction may cause atrophy of the mucosa.

Uses: In upper respiratory infection, allergic and vasomotor rhinitis, sinusitis and blocked eustachian tubes: nasal decongestants afford symptomatic relief.

ANORECTIC AGENTS (ANOREXIANTS)

- Though amphetamine suppresses appetite, it is not recommended for the treatment of obesity due to its central stimulant effects.
- Many amphetamine—like drugs which suppress appetite but lack significant CNS stimulant effects are now available.
- They are **fenfluramine, dexfenfluramine, mazindol, phenylpropanolamine** and others.

Mechanism of action: Increases 5HT neurotransmission in hypothalamus.

Adverse effects include risk of abuse, drowsiness and depression because of these adverse effects they are only used for short periods as adjuncts to other measures.

SELECTIVE β_2 STIMULANTS (bronchodilators)

- It includes: orciprenaline, salbutamol, terbutaline and salmeterol.
- **Pharmacological effects:** The adrenergic agents are primarily β_2 -agonists.
- They are smooth muscle relaxants which produce bronchodilatation, vasodilation and uterine relaxation without significant cardiac stimulation.

Therapeutic uses: These agents are used therapeutically for the treatment of bronchial asthma or bronchospasm, where their lack of cardiac stimulation is a key advantage. Experts recommend regular use of inhaled corticosteroids to decrease inflammation and as-needed use of β_2 -agonists to control acute symptoms. They can be given by inhalation and are used:

1. In bronchial asthma
2. As uterine relaxants to delay premature labor.

Administration: β_2 -stimulating bronchodilators are used chiefly as aerosol inhalants; oral and injectable forms are also available.

Adverse effects of the β_2 -agonists are similar to those seen with the sympathomimetic drugs listed previously.

- Regular use of a short-acting β_2 -agonist can be associated with increased bronchial hyperresponsiveness to methacholine challenge.
- Overuse of β_2 -agonists by patients with asthma has been associated with increased mortality.
- Even though their effects are primarily bronchial, β_2 -agonists should be used with caution in patients with cardiovascular disease or hyperthyroidism because they can have minimal effects on the β_1 -receptors of the heart.

Adrenergic Antagonists (Sympatholytics)

- This class of drugs are also called; sympatholytics, anti-adrenergic agents, and adrenergic blocking drugs.
- Adrenergic antagonists bind to the adrenergic receptors and prevent the action of adrenergic agonists. They may block either alpha or beta receptors or both.

ALPHA ADRENERGIC BLOCKING AGENTS

Alpha receptor antagonists block the adrenergic responses mediated through alpha adrenergic receptors. Some of them have selectivity for α_1 - or α_2 -receptors.

Actions

The important effects of α receptor stimulation are:

1. α_1 (postsynaptic) mediated vasoconstriction
 2. α_2 (presynaptic) receptor mediated inhibition of noradrenaline release.
- The result of alpha receptor blockade by α -antagonists are:
 1. α_1 -blockade inhibits vasoconstriction leading to vasodilatation and thereby ↓BP. This fall in BP is opposed by the baroreceptor reflexes which tend to ↑heart rate and cardiac output.
 2. α_2 -blockade enhances ↑release of NA which stimulates β_1 -receptors in heart results in tachycardia and receptors cardiac output.
 - Thus, the predominant effect of α -blockade is hypotension with tachycardia.
 - Selective α_1 -blockade results in hypotension without significant tachycardia.
 - Selective α_2 -blockade ↑NA release resulting in hypertension.
 - α -blockade also results in miosis and nasal stuffiness. α -blockade in the bladder and prostate leads to decreased resistance to the flow of urine. Therefore, they can be used for treatment of BPH in old age males.

Classification

1. Non-selective
 - a. *Non-equilibrium type blockers.* Phenoxylbenzamine
 - b. *Competitive (Equilibrium type) blockers.* Ergot alkaloids (ergotamine), Tolazoline, Phentolamine, Ketanserin.
2. Selective
 - a. α_1 -blockers. Prazosin, Terazosin, Doxazosin.
 - b. α_2 -blocker. Yohimbine

Phenoxylbenzamine

Mechanism of action

- Phenoxylbenzamine is a haloalkylamine and is closely related to the nitrogen mustards.
- It binds covalently to the α -receptor, producing an irreversible blockade.
- Phenoxylbenzamine is somewhat more potent in blocking α_1 (postsynaptic)-receptors than in blocking α_2 (presynaptic)-receptors.
- The action lasts for 3-4 days. It also partially blocks histamine, 5-HT and cholinergic receptors at higher doses, but not to β -adrenergic receptor.

Pharmacological effects: Phenoxylbenzamine antagonizes sympathetic responses mediated by α -adrenergic receptors.

1. **Cardiovascular effects:** Phenoxylbenzamine induces postural hypotension caused by a lack of compensatory sympathetic vasoconstriction. In addition, it increases cardiac output and decreases total peripheral resistance.
2. **CNS effects:** Phenoxylbenzamine stimulates the CNS, producing nausea, hyperventilation, and loss of time perception.
3. Most metabolic effects produced by catecholamines are the result of their effects on β -receptors; thus α -adrenergic blocking agents do not have significant **metabolic actions**.

Therapeutic use: Phenoxybenzamine is used

- To reverse vasoconstriction in shock (if it is used in shock, the patient must have an elevated central venous pressure).
- For acute hypertensive episodes caused by use of sympathomimetics or MAO inhibitors, or by pheochromocytomas.
- For control of autonomic hyperreflexia resulting from spinal cord transection.
- To relieve vasospasm in Raynaud's phenomenon.

Adverse effects

- Nausea and vomiting may occur with oral administration.
- Injections cause local tissue irritation.
- Miosis and nasal stuffiness may occur.
- Postural hypotension and reflex tachycardia may occur, especially in patients who are hypovolemic.
- Ejaculation may be inhibited.

Ergot Alkaloids

- Ergotamine, ergotamine and their derivatives are competitive antagonists and the blockade is of short duration.
- Some of them have a direct stimulant effect on smooth muscles : cause contraction of the uterus and ↑BP due to vasoconstriction.
- Prolonged use of these can cause gangrene of the toes and fingers.

Mechanism of action

- These agents are weak α -adrenergic blockers and are serotonin antagonists.
- They are also partial agonists at α -adrenergic receptors and agonists at tryptaminergic and dopaminergic receptors.

Pharmacological effects

- They directly stimulate smooth muscles.
- Ergot alkaloids are CNS stimulants and, therefore, may cause effects such as confusion, irregular respiration and anxiety.
- They cause significant elevation of blood pressure via peripheral vasoconstriction.

Therapeutic uses

- Ergotamine tartrate, by virtue of its vasoconstricting effects, is used in the treatment of migraine headaches.
- Ergonovine maleate is a powerful oxytocic but lacks the adrenergic blocking activity of ergotamine. It causes direct contraction of uterine smooth muscle and is used to decrease postpartum bleeding.

- Methylergonovine maleate is also used to decrease postpartum uterine bleeding.
- Methysergide is used for prophylaxis of migraine attacks.

Adverse effects

- Ergot preparations often cause nausea and vomiting. Their vasoconstricting effects can cause vascular insufficiency, leading to gangrene.

Phentolamine and Tolazoline

- Phentolamine and tolazoline are imidazoline derivatives. They are competitive α -blockers.
- In addition they also block 5-HT receptors, stimulate gut motility and ↑gastric secretion.

Pharmacological effects

- These agents produce vasodilation and reflex cardiac stimulation.
- They decrease peripheral resistance and increases venous capacity.
- Both stimulate salivary, lacrimal, pancreatic, and respiratory tract secretions.
- They cause a gastric secretion that induces effects similar to those of histamine.
- Phentolamine is more potent than tolazoline.
- Tolazoline is absorbed when given orally and is rapidly excreted by the kidneys; phentolamine is excreted more slowly. Both can be given parenterally.

Therapeutic uses

- Phentolamine has been used to control acute hypertensive episodes caused by use of sympathomimetics.
- In the past, phentolamine was used as a diagnostic test for pheochromocytoma, but it has been replaced by assays for urinary catecholamines.
- Tolazoline can be used in the treatment of neonates with persistent pulmonary hypertension, despite use of oxygen therapy and mechanical ventilation.
- Tolazoline has been used experimentally to relieve vasospasm and in the treatment of Raynaud's phenomenon.

Adverse effects

- Both drugs can cause cardiac stimulation, leading to arrhythmias and anginal pain, especially after parenteral administration; they must be used with caution in patients with coronary artery disease.
- Because they induce gastrointestinal stimulation, both drugs must be used with caution in patients with peptic ulcer disease.
- Tolazoline can produce a paradoxical hypertension.

Prazosin

- It is a potent, highly selective, postsynaptic α_1 -blocker with 1000 times greater affinity for α_1 -receptors.
- Arterioles are dilated more than veins resulting in hypotension. There is no significant tachycardia (as α_2 -receptors are spared there is no $\uparrow$ in NA release).
- It is orally effective and is metabolized in the liver.

Pharmacological effects

- Prazosin reduces vascular tone in both resistance and capacitance vessels.
- Because prazosin has no effect on α_2 -receptors, neurotransmitter feedback inhibition is maintained, so that prazosin causes only a small degree of tachycardia.
- It decreases arterial pressure without change in cardiac output, heart rate, and right atrial pressure.
- In addition it may decrease central sympathetic outflow.
- Prazosin also inhibits phosphodiesterase, the enzyme that degrades cAMP resulting in $\uparrow$ cAMP which also contributes to vasodilation.
- Used in - Hypertension, LVF and Raynaud's disease

Adverse effects

- First dose phenomenon: 1 hour after the initial dose, marked postural hypotension occurs which may lead to fainting.
- To avoid this, prazosin should be started with a low dose and taken at bed time.

Terazosin is longer-acting and can be given once daily.

Yohimbine

- It is a relatively selective α_2 -blocker which increases BP and heart rate due to NA release.
- It causes congestion of genitalias for which it is used to treat psychogenic impotence.
- It is also claimed to be an aphrodisiac though the effect is only psychological.

Uses of α -blockers

Pheochromocytoma: It is an adrenal medullary tumor which secretes large amounts of catecholamines resulting in hypertension. The tumor has to be removed surgically. Phenoxybenzamine and phentolamine are used for the preoperative management of the patient and during the operation.

Hypertension: Selective α_1 -blockers like prazosin are used in the treatment of hypertension. Phenoxybenzamine or phentolamine can be used in hypertensive crisis.

Peripheral vascular diseases: Like Raynaud's phenomenon may be benefited by α -blockers which afford symptomatic relief.

Benign prostatic hypertrophy(BPH): Blockade of α_1 receptors in the bladder, prostate and urethra reduce resistance to urine outflow. Prazosin is useful in patients who cannot be operated upon.

Congestive cardiac failure: Because of its vasodilator action, prazosin is useful in CCF. But ACE inhibitors are preferred.

BETA-ADRENERGIC BLOCKING DRUGS

β -blockers are drugs that block the actions of catecholamines mediated through the β -receptors.

Classification

1. Non-selective:

- Without intrinsic sympathomimetic activity (PSNT)
 - Propranolol, Sotalol, Nadolol, Timolol.
- With intrinsic sympathomimetic activity (POA)
 - Pindolol, Oxprenolol, Alprenolol.
- With additional alpha blocking property
 - Labetalol, Carvedilol.

2. (β_1) Selective or Cardioselective: Metoprolol, Atenolol, Acebutolol, Esmolol

3. (β_2) Selective: Butoxamine

Pharmacological Actions

1. CVS: β -blockers decrease heart rate, force of contraction and cardiac output. Blood pressure falls. The effect is more pronounced in presence of increased sympathetic tone than in a normal situation.

AV conduction is delayed. Myocardial oxygen requirement is reduced due to reduced cardiac work. It also improves exercise tolerance in angina patients.

High doses produce membrane—stabilising activity like quinidine causing direct depression of the heart.

2. Metabolic: β -antagonists block lipolysis and glycolysis induced by sympathetic stimulation. Plasma triglycerides may increase and HDL levels decrease in some patients.

3. Respiratory tract: Blockade of β_2 -receptors in the bronchial smooth muscle causes increase in airway resistance—may precipitate acute attack in asthmatics.

4. **Eye:** Many β -blockers reduce intraocular pressure by decreased secretion of aqueous humor $\downarrow$ (IOT).

Pharmacokinetics

- Although propranolol is completely absorbed from the gastrointestinal tract, a large portion of the drug is extracted by the liver before it enters the systemic circulation.
- Wide variation in the hepatic metabolism of the drug among individuals causes significant differences in the plasma concentrations attained.
- Propranolol is approximately 90% bound to plasma proteins.
- The elimination half-life is approximately 3 hours for a small dose, but it is prolonged with larger doses and is significantly prolonged in the presence of cirrhosis.
- A metabolic product, 4-hydroxypropranolol, is active but has a short half-life.

Adverse Reactions

- Rash, fever, and purpura are characteristic of an allergic response and require discontinuation of the drug.
- **Bradycardia** is common. Patients with AV conduction defects may develop arrhythmias with β -blockers.
- **CCF:** In patients with impaired myocardial function, sympathetic activity supports the heart. β -blockade eliminates this and may precipitate CCF.
- β -blockers can precipitate **acute asthmatic attack** and is contraindicated in asthmatics.
- **Cold extremities** especially in patients with peripheral vascular disease may occur.
- **CNS** Sedation, depression and rarely hallucinations can follow the use of β -blockers.
- Rapid withdrawal can lead to “supersensitivity” of β -adrenergic receptors, which can provoke anginal attacks, arrhythmias, or myocardial infarction. Abrupt withdrawal of β -blockers after prolonged use can also cause **rebound hypertension**. This is due to up-regulation of β receptors. Hence β -blockers should be gradually tapered.
- **Metabolic effects** Weakness, $\downarrow$ exercise capacity may be seen due to its metabolic effects. Because of its effects on carbohydrate metabolism, the hypoglycemic action of insulin may be augmented. Therefore, diabetics being treated with insulin and persons prone to hypoglycemia must use propranolol with caution.
- Prolonged use may cause fatigue, depression, nightmares, sexual dysfunction, and peripheral arterial insufficiency.

- Because of its effects on peripheral blood flow, propranolol is contraindicated in patients with Raynaud’s phenomenon.

Some Important Drug Interactions

1. Propranolol + Insulin – when diabetics on insulin also receive propranolol:
 - i. β -blockade masks tachycardia which is the first warning signal of hypoglycemia.
 - ii. β -blockade delays the recovery from hypoglycemia by preventing glycogenolysis induced by sympathetic stimulation. This may be avoided by using a β_1 -selective blocker.
2. β -blockers + Catecholamines – in patients on nonselective β -blockers, blockade of vascular β -receptors could predispose peripheral vessels to intense vasoconstriction (receptor up regulation) from even small doses of adrenaline used with LAs. Hence it is safer to use plain local anesthesia in such patients.
3. Propranolol + Verapamil – since both cause myocardial depression, profound depression may result. Hence the combination should be avoided.

Cardioselective β -blockers, e.g. Atenolol, Metoprolol, Esmolol. These drugs:

- Selectively block β_1 -receptors, β_2 -blockade is weak.
- Bronchospasm is less/negligible.
- Inhibition of glycogenolysis is lower – hence safer in diabetics.
- Exercise performance impaired to a lesser degree.
- Reduced chances of peripheral vascular disease.

Some individual β -antagonists

Atenolol

- Selective β_1 -blocker.
- Longer-acting – given once daily.
- It is less lipid soluble – dose not cross BBB – hence no CNS side effects.
- No side effects on lipid profile.

Metoprolol: It is a selective β_1 -adrenergic antagonist.

Pharmacological effects

- Metoprolol inhibits the inotropic and chronotropic cardiac responses to isoproterenol.
- It is 1/50th as potent as propranolol in inhibiting the vasodilator response to isoproterenol; however, it is long-acting.
- It is absorbed well when given orally.

Therapeutic uses: Metoprolol is used chiefly in the treatment of hypertension.

Adverse effects

- Metoprolol produces fewer deleterious effects in asthmatic patients because of its selective β_1 -adrenergic antagonism, but its use in asthmatics still requires caution.
- Other adverse effects are similar to those of propranolol.

Esmolol

- Selective β_1 -blocker
- Ultra short-acting – $t_{1/2}$ - 8 minutes.
- Used IV (parenteral)
- Safer in critically ill patients and in emergencies when immediate β -blockade is needed.

Timolol

- Non selective, short-acting β -blocker
- Used in glaucoma - as eye drops.

Uses of β -blockers

1. **Hypertension:** β -blockers are useful in the treatment of mild to moderate hypertension. A β -blocker can be used alone or with other antihypertensive drugs.
2. **Chest pain (Angina):** β -blockers are useful in the prophylaxis of exertional angina. Both the severity and frequency are reduced. They reduce both cardiac work and O_2 demand.
3. **Arrhythmias:** β -blockers are useful in the treatment of both ventricular and supraventricular arrhythmias. Sotalol has additional antiarrhythmic effects.
4. **Ischemic Heart Diseases (IHD), i.e. Myocardial infarction:** β -blockers in acute MI may limit the size of the infarct. In patients recovered from MI, long-term treatment with β -blockers prolongs survival.
5. **Obstructive cardiomyopathy:** β -blockers are found to be beneficial.
6. **Pheochromocytoma:** Propranolol is given with α -blockers before surgery to control hypertension.
7. **Thyrotoxicosis:** Propranolol controls palpitation, tremors and affords symptomatic relief in thyrotoxicosis; it is used as an adjuvant.
8. **Glaucoma:** Timolol is used topically in open angle glaucoma. Newer β -blockers are now developed.
9. **Migraine (Prophylaxis):** Propranolol reduces frequency and severity of migraine headache therefore it is used for prophylaxis.

10. **Stress and Anxiety:** Propranolol prevents the acute panic symptoms seen in public speaking, examination and other such anxiety-provoking situations. Performance in musicians can be improved. Tremors, Palpitations, tachycardia and other symptoms of sympathetic over activity are alleviated.

Doses of some β -blockers

Drug	Total daily dose (mg)	Frequency
Propranolol (INDERAL)	40-240	
Metoprolol (MEFOCARD)	100-200	
Atenolol (ATEN)	25-100	once daily
Pindolol (PINADOL)	10-45	6 hourly

Alpha and Beta-adrenergic Blockers

Labetalol: Blocks both α_1 and β (β_1 and β_2) receptors. It is a competitive antagonist. Heart rate, contractility, AV conduction and BP fall. Blood flow to the limbs increases. It is a nonselective β -blocker, which also has α_1 -blocking activity. It is used in the treatment of mild to severe hypertension.

- Labetalol reduces peripheral vascular resistance while preventing reflex tachycardia.
- When combined with either prazosin or hydralazine, labetalol is faster acting than other α -blockers.
- It can be given intravenously in hypertensive emergencies.
- *Adverse effects.* Labetalol may cause postural hypotension and jaundice in addition to the adverse effects seen with other α -blockers. GI disturbances and other effects of alpha and β -blockade.

Uses: Labetalol is used in hypertensive emergencies and pheochromocytoma.

Carvedilol and **mecroxalol** also are alpha and β -antagonists. They have additional anti-oxidant property.

Nadolol: It is a nonselective β -adrenergic blocking agent that is not metabolized and is excreted unchanged in the urine. Its effect and adverse reactions are similar to those of propranolol.

Sotalol: It is a nonselective β -blocker without intrinsic sympathomimetic or local anesthetic activity. It is approved for the treatment of life-threatening ventricular arrhythmias.

Pindolol: It is a nonselective β -blocker, which also has some degree of intrinsic sympathomimetic (α -adrenergic) activity. Unlike the case with propranolol, no rebound tachycardia occurs upon abrupt withdrawal of pindolol.

Acebutolol: It is a β -blocker with mild intrinsic sympathomimetic activity (ISA).

- Its β_1 -blocking effects exceed its β_2 -blocking effects.
- Because of its ISA, it may not cause as slow bradycardia as propranolol does.
- Adverse effects, in addition to those seen with other β -blockers, include arthritis, myalgia and arthralgia, and the presence of antinuclear antibodies.

Betaxolol is a selective β_1 -adrenergic antagonist that is administered once daily. It is more lipophilic than atenolol. It is also available as a topical formulation for the treatment of glaucoma.

Cholinergic System and Drugs

Acetylcholine (ACh) is a quaternary ammonium ester of choline that is rapidly hydrolyzed by acetylcholinesterase and plasma cholinesterase. It is an important neurotransmitter of the ANS. The nerves that synthesize, store and release ACh are called '**Cholinergic nerve**'.

Synthesis of ACh: Acetylcholine is synthesized from acetyl-CoA and choline, catalysed by the enzyme [CAT] choline acetyltransferase. This ACh is stored in small vesicles (synaptic vesicles) in the cholinergic nerve terminals called terminal buttons.

The sites of release of acetylcholine are:

1. *Skeletal muscles.* Somatic nerves supplying skeletal muscles.
2. *Ganglia.* All the preganglionic fibres of ANS, i.e. at both the sympathetic and parasympathetic ganglia.
3. The postganglionic parasympathetic nerve endings.
4. *Sweat glands.* The sympathetic postganglionic nerve endings.
5. *Adrenal medulla. (Presynaptic)*
6. *CNS.* Brain and spinal cord.

Transmission of an Impulse

- When an action potential reaches the presynaptic membrane, ACh is released into the synaptic cleft.
- This ACh binds to and activates the cholinergic receptor on the postsynaptic membrane leading to the depolarization of postsynaptic membrane. Thus the impulse is transmitted across the synapse.
- ACh released into the synaptic cleft is rapidly destroyed by the acetylcholinesterase (AChE) enzyme. Then the postsynaptic membrane is repolarised (Fig. 2A.5.1).

Cholinesterases: Acetylcholine is hydrolyzed to choline and acetic acid by the enzymes cholinesterases. Two types of AChE are present:

1. **True cholinesterase** – at neurons (synapse), RBC, ganglia and neuromuscular junction.

2. **Pseudocholinesterase** – in plasma, liver, intestine, glial cells and other organs.

True choline esterase hydrolyses ACh very fast within microseconds, it also hydrolyses methacholine, while pseudocholine esterase hydrolyses ACh slowly within minutes. It hydrolyses butyrylcholine and benzoylcholine but does not hydrolyse methacholine.

Cholinergic Receptors

There are two classes of cholinergic receptors (Table 2A.5.1):

- a. **Muscarinic** and
- b. **Nicotinic**

Muscarinic receptors: There are five subtypes of muscarinic receptors ($M_1 - M_5$). They are located in the heart, smooth muscles, glands, eyes and CNS.

Table 2A.5.1: Subtypes and location of cholinergic receptors

	Subtype	Location
Nicotinic	N_M	Neuromuscular junction
	N_N	Autonomic ganglia (all) Adrenal medulla, CNS
Muscarinic	M_1	Autonomic ganglia, gastric glands, CNS
	M_2	Heart, nerves
	M_3	Glands, smooth muscles
	M_4	CNS
	M_5	CNS

Nicotinic receptors: Two subtypes of nicotinic receptors are identified. N_N receptors at the autonomic ganglia and adrenal medulla and N_M receptors are present at the skeletal muscle end plate.

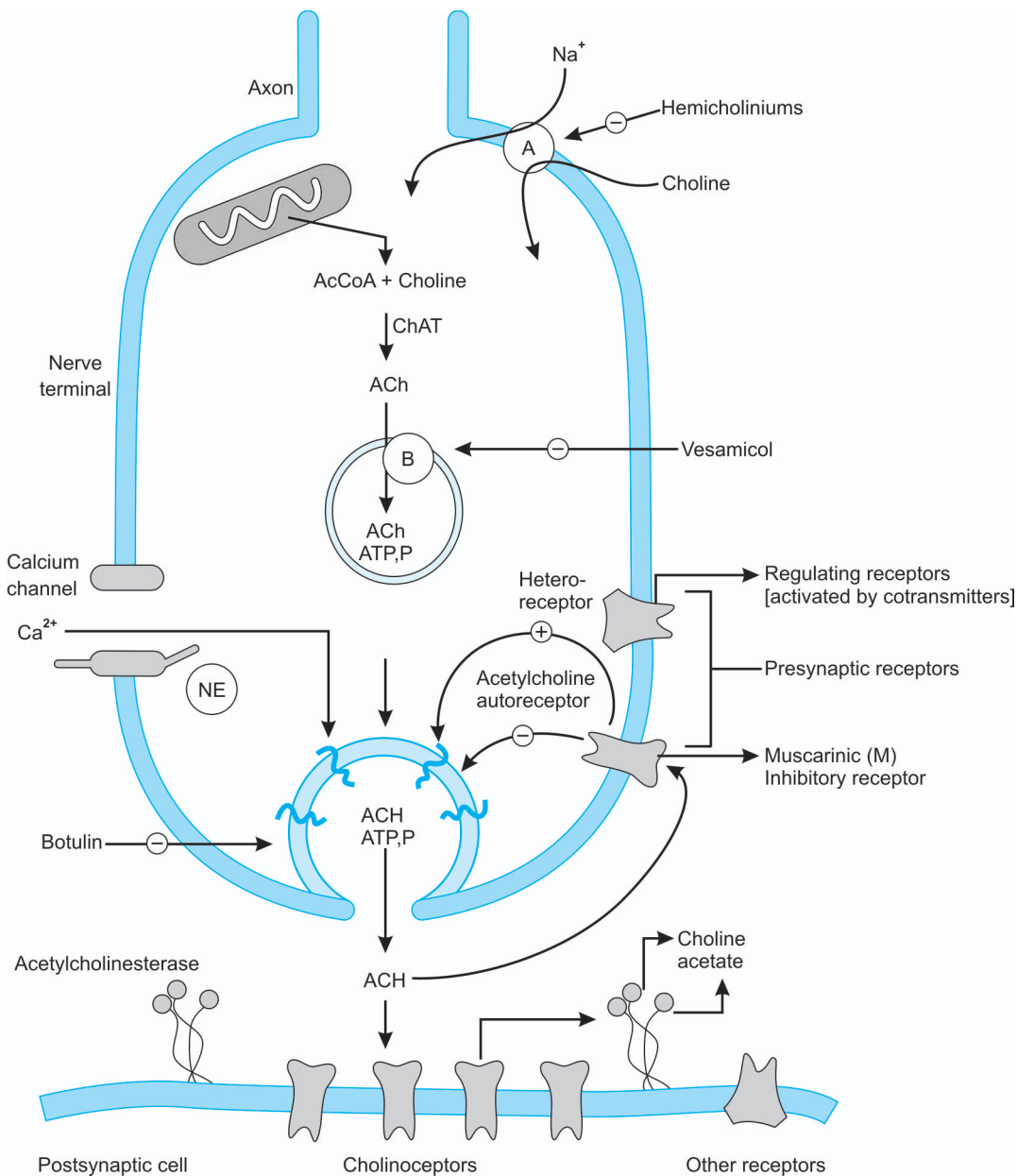


Fig. 2A.5.1: Neurohumoral transmission of Acetylcholine with various steps and also drug affecting them

PHARMACOKINETIC

- Choline-esters (ACh) has low lipid solubility therefore:
 - Poor GIT absorption
 - Does not cross blood brain barrier.
- Hydrolysis (by Choline-esterase) is variable, i.e.
 - ACh hydrolysed quickly (Fig. 2A.5.2)
 - Carbachol and bethanechol fairly resistant to hydrolysis.

PHARMACODYNAMICS

Cellular and molecular pharmacology (mechanism of action)

- M receptor**
 - Increased concentration of second messenger cGMP.
 - Decreased concentration of cAMP. (affirmation)
 - Increase in cytosolic calcium concentration.
 - Increase in potassium influx.

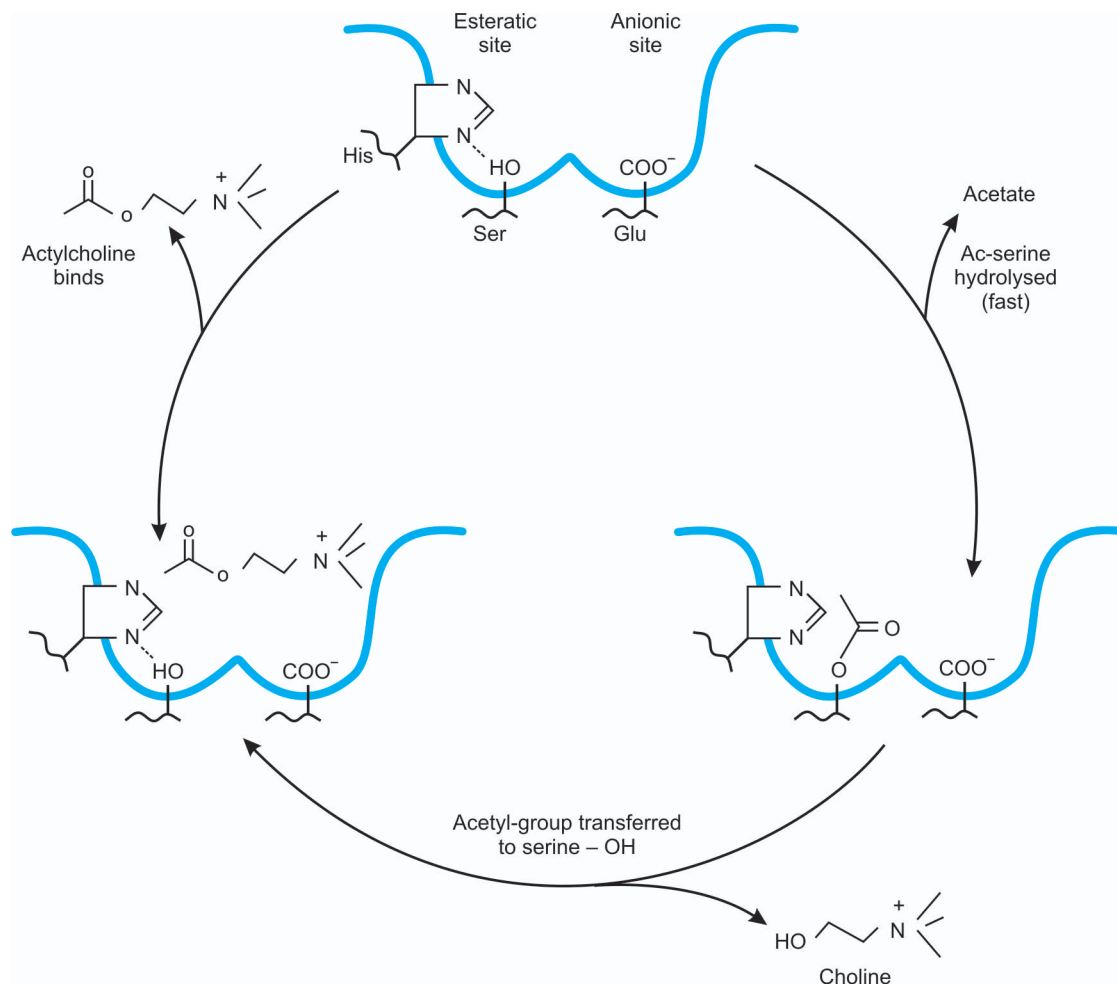


Fig. 2A.5.2: Mechanism of Acetylcholine hydrolysis by Acetylcholinesterase

• **N receptor**

1. It is opening increases influx of Na^+ , K^+ , Ca^{++} channels.

PHARMACOLOGICAL ACTIONS OF ACETYLCHOLINE

Acetylcholine is taken as the prototype of parasympathomimetic drugs. Acetylcholine binds with muscarinic and nicotinic receptors and produces its specific actions.

Muscarinic Actions [through M receptors]: Muscarinic actions resemble the actions of the alkaloid muscarine found in some mushrooms.

CVS and Heart:

- Acetylcholine produces:
 - a. A negative inotropic ($\downarrow$ force of contraction) effect reduces contractility.
 - b. A negative chronotropic (reduces heart rate) effect i.e. bradycardia.
 - c. Vasodilation

- There occur fall in cardiac output (some time cardiac arrest may occur).
- Its actions on the heart are the same as the effects of vagal stimulation.
- Large intravenous doses cause an increase in blood pressure because there is release of catecholamines from the adrenal medulla and activation of sympathetic ganglions.

Blood vessels: ACh relaxes the vascular smooth muscles and dilates the blood vessels of the skin and mucous membrane. The BP falls due to a fall in total peripheral resistance. The muscarinic receptors are present in blood vessel but there is no cholinergic innervations.

- The vasodilation occurs because of release of free NO (nitric oxide) which is a EDRF (endothelial derived relaxing factor)

Smooth muscles: ACh increases the tone of all other smooth muscles.

- **Gastrointestinal tract** – tone and peristalsis is enhanced, sphincters are relaxed, resulting in rapid forward propulsion of intestinal contents.
- **Bronchial smooth muscle** – contracts resulting in bronchospasm.
- **Urinary bladder** – detrusor contracts and trigonal sphincter relaxes – promotes voiding of urine.

Secretory Glands: Acetylcholine enhances the secretions of all glands; salivary, lacrimal, nasopharyngeal, tracheo-bronchial, gastric and intestinal secretions are increased. Sweating is also increased. Enhanced bronchial secretions and bronchospasm result in severe dyspnea.

Eye: Constriction of pupil (miosis) by contracting the circular muscles of the iris. Ciliary muscle contracts resulting in spasm of accommodation.

Nicotinic Actions [through N receptors]: These effects resemble the actions of the alkaloid nicotine.

Neuromuscular junction: (Through N_M receptors) ACh brings about contraction of skeletal muscles. Large doses cause persistent depolarization of skeletal muscles resulting in paralysis.

Autonomic ganglia: (Through N_N receptor) ACh stimulates sympathetic and parasympathetic ganglia and the adrenal medulla.

CNS: ACh is a neurotransmitter at several sites in the CNS. Its important actions are summarized later on.

CHOLINERGIC DRUGS

Cholinergic drugs are chemicals that act at the same site as acetylcholine and thereby mimic its actions. They are therefore called parasympathomimetics or cholinomimetics.

Cholinergic drugs may be classified as:

1. **Esters of choline** – Acetylcholine, Methacholine, Carbachol, Bethanechol
2. **Cholinomimetic alkaloids** – Pilocarpine, Muscarine, and arecholine.
3. **Anticholinesterases:**
[Reversible – Neostigmine, Physostigmine]
[Irreversible – Organophosphorus compounds].

CHOLINOMIMETIC ALKALOIDS

Methacholine (acetyl- β -methylcholine):

- **Chemistry:** Methacholine differs chemically from acetylcholine by the addition of a methyl group to the β position of choline. As a result:
 - Methacholine is hydrolyzed only by *acetylcholinesterase* and, therefore, has a longer duration of action than acetylcholine.
 - It becomes a pure muscarinic-acting agent.

- **Pharmacologic effects:** The effects of methacholine on the *cardiovascular system and other systems are similar to those of acetylcholine.*

Carbachol (carbamylcholine)

- Carbachol has a carbamic acid-ester link, which is not readily susceptible to hydrolysis by cholinesterases.
- Carbachol has all the pharmacologic properties of acetylcholine. It exerts both nicotinic and muscarinic effects.
- Carbachol is used **ophthalmically as a miotic agent.**

Bethanechol

- Chemically, bethanechol has the structural features of both methacholine and carbachol. It is resistant to hydrolysis by cholinesterases and is mainly muscarinic in action.
- Bethanechol shows no negative inotropic or chronotropic cardiovascular effects.
- It is used therapeutically for **abdominal distention, esophageal reflux, and urinary bladder distention.**

Pilocarpine

- It is a tertiary amine alkaloid obtained from the leaves of *Pilocarpus microphyllus*. Like ACh it stimulates cholinergic receptors, but its muscarinic actions are prominent.
- Its actions are similar to those of methacholine. When applied locally to the eye, it causes miosis, spasm of accommodation and a fall in intraocular tension (pressure).
- Its major therapeutic indication is in the treatment of **glaucoma** (0.5-4% eye drops). It also increases sweat (diaphoretic) and salivary secretions (sialogogue).

Adverse effects: When used as eye drops, burning sensation and painful spasm of accommodation can occur.

GLAUCOMA

It is an eye disease characterized by increased (> 20 - 22 mmHg) intraocular pressure. If untreated, irreversible damage can occur, as optic nerve degenerates leading to permanent blindness. Glaucoma is of two types:

- **Acute congestive/narrow angle glaucoma:** In this, iris blocks the drainage of aqueous humor at the canal of Schlemm leading to increased intraocular pressure. It needs immediate treatment.
- **Chronic simple/open angle glaucoma:** Onset is slow; needs long-term treatment. Surgery is the preferred. It is actually degenerative disease affecting trabecular meshwork.

Treatment: See Figure 2A.5.3.

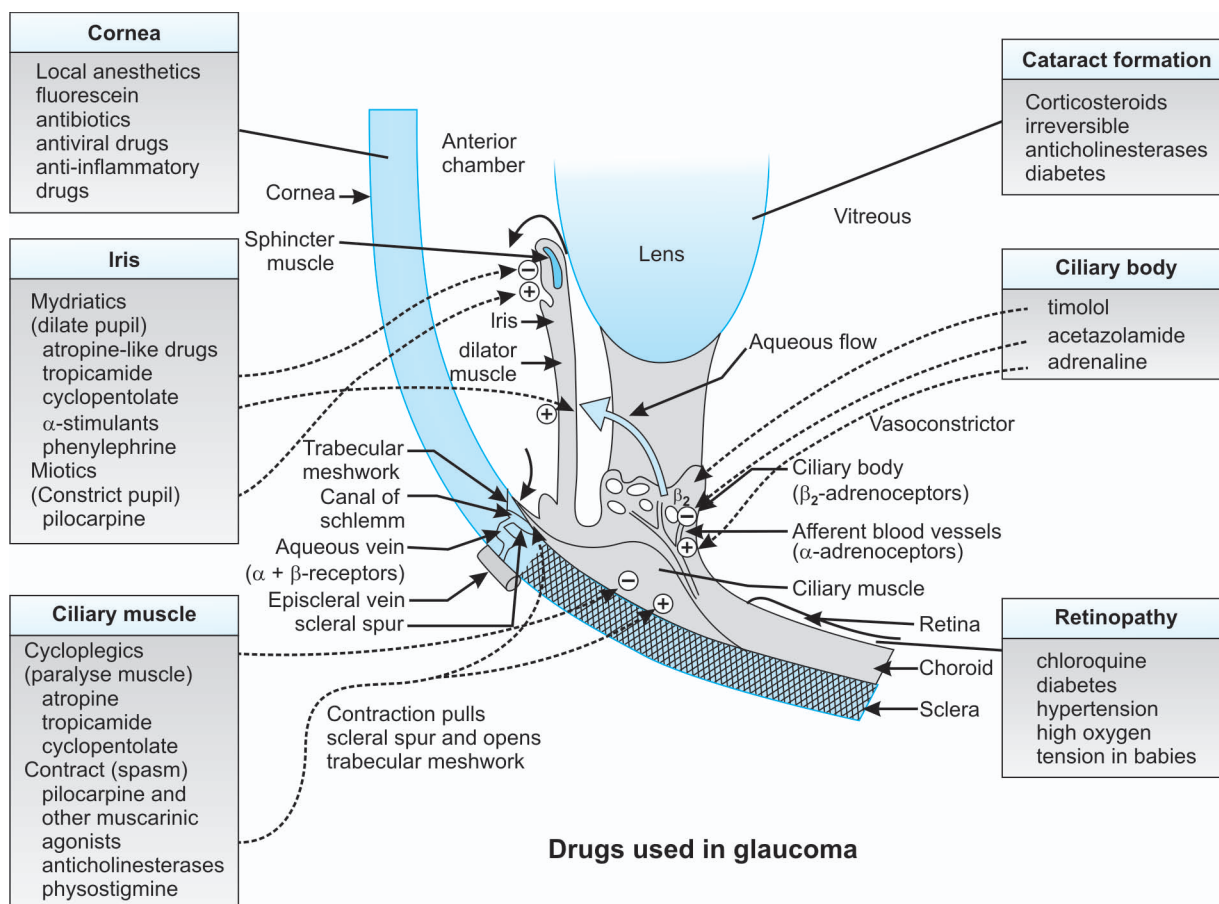


Fig. 2A.5.3: Classification, sites and mechanism of the drugs used in various ophthalmic dysfunctions including glaucoma

Uses of cholinomimetics

- Acetylcholine is destroyed in the gut when given orally. On intravenous administration, it is rapidly metabolized by pseudocholinesterases in the plasma and by the cholinesterase at the site of action. Therefore, it is not used therapeutically.
- Among the cholinesterase, methacholine is rarely used.
- Carbachol and pilocarpine are used in glaucoma.
- Bethanechol may be used in some cases of postoperative paralytic ileus and urinary retention.
- Arecoline. It is present in catechu, possesses both nicotinic and muscarinic action and has prominent CNS action. It is an enhancer of cognitive function. It has no therapeutic use but can be tried in dementia.
- Oxetremorine. It is a synthetic compound. Specifically act on M receptor. It can also produce parkinsonism like extrapyramidal effects. Its use is now restricted only for experimental tool.

ANTICHOLINESTERASES

Anticholinesterases (antiChEs) or cholinesterases inhibitors are drugs which inhibit the enzyme cholinesterase. As their structure resembles that of ACh, they bind to AChEs and inactivate them.

Acetylcholine



Choline + Acetic acid

Thus, ACh is not hydrolysed and it accumulates. The actions of these drugs are due to this accumulated ACh. Hence, the actions are similar to cholinergic agonists.

Anticholinesterases may be:

- Reversible:** Physostigmine, Neostigmine, Edrophonium, Echothiophate
- Irreversible:** Organophosphates – Malathion, Sumithion, Toxic nerve gases.

ANTICHOLINESTERASE AGENTS

Anticholinesterases inhibits the action of Acetylcholinesterase, and therefore ultimately prolong and potentiate the concentration of Acetylcholine.

Physostigmine: It is an alkaloid obtained from the plant *Physostigma venenosum*. It is a tertiary ammonium compound – hence has better penetration into tissues and it also crosses the BBB.

Mechanism of action: This alkaloid forms a reversible complex at the site of acetylcholinesterase where acetylcholine is broken down.

Pharmacokinetics: Physostigmine is well absorbed from the gastrointestinal tract, subcutaneous tissues, and mucous membranes.

Pharmacological effects: The pharmacologic properties of physostigmine mimic those of acetylcholine.

- It produces miosis and, thus, can antagonize the mydriasis induced by atropine.
- When given in large doses, it causes fasciculation, then paralysis, of skeletal muscles.

Therapeutic uses: It is used in

- Treatment of atropine, phenothiazine, and tricyclic antidepressant intoxication
- Treatment of glaucoma, especially simple and secondary glaucoma. It is available as 0.1-1% eye drops.
- Treatment of early stages of Alzheimer's disease.

Neostigmine

Chemistry: Neostigmine is a synthetic reversible anticholinesterase that contains a quaternary nitrogen.

Pharmacokinetics

- Neostigmine is not well absorbed orally.
- It does not penetrate the blood-brain barrier, which minimizes the toxicity.
- It is destroyed by plasma esterases and is excreted in the urine.

Pharmacological effects

- The pharmacological properties of neostigmine mimic those of acetylcholine.
- It also has direct action on nicotinic receptors, in addition to blocking acetylcholinesterase.
- It reverses the neuromuscular blockade produced by curare and its derivatives.

Therapeutic uses

- Neostigmine is used to reverse the effects of competitive neuromuscular blocking.
- It is used in the management of paralytic ileus and atony of the urinary bladder.

- It is also used in the symptomatic treatment of myasthenia gravis.

Edrophonium

Pharmacokinetics: Edrophonium is more rapidly absorbed and has a shorter duration of action than neostigmine. It is administered parenterally.

Therapeutic uses include:

- Diagnosis of myasthenia gravis.
- Antagonism of curare-like agents.
 - *Pyridostigmine*: less potent and long acting.
 - *Ambenonium*: Potent and long acting, used in treatment of myasthenia gravis.
 - *Edrophonium*: short acting therefore used for diagnostic purpose in myasthenia gravis.
 - *Tacrine*: Long acting, crosses BBB, cognition enhancer therefore used in the treatment of Alzheimer's disease.
 - *Rivastigmine*: Lipophilic, cognition enhancer, improve behavior
 - *Donepezil*: Lipophilic, cognition enhancer, improve behavior, therefore both are used in the treatment of Alzheimer's disease.
 - *Demecarium*: Potent and long acting, used as a miotic agent.
 - *Echthiophate*: quaternary structure, used in the treatment of glaucoma.

Uses of Anticholinesterases

1. As a miotic: Physostigmine causes miosis, spasm of accommodation and a ↓ IOP. It is used in:

- Glaucoma – can be used with pilocarpine for better effect
- Alternately with a mydriatic to break adhesions between the iris and the lens.

2. Myasthenia gravis (MG):

- It is a chronic autoimmune disease characterized by progressive weakness with rapid and easy fatigability of skeletal muscles.
- Antibodies to nicotinic receptors are found, resulting in a decrease in the number of these receptors at NMJ [Neuromuscular junction]. Neostigmine (15 mg tab 6 hrly) or pyridostigmine or a combination of these may be given.
 - Edrophonium is used for the diagnosis.
 - In addition to its anti ChE activity, neostigmine directly stimulates the nicotinic receptors and increases the amount of ACh released during each nerve impulse.
 - AntiChEs enhance ACh levels at NMJ (Neuromuscular junction) by preventing its destruction. They thus increase the force of contraction and improve muscle power.

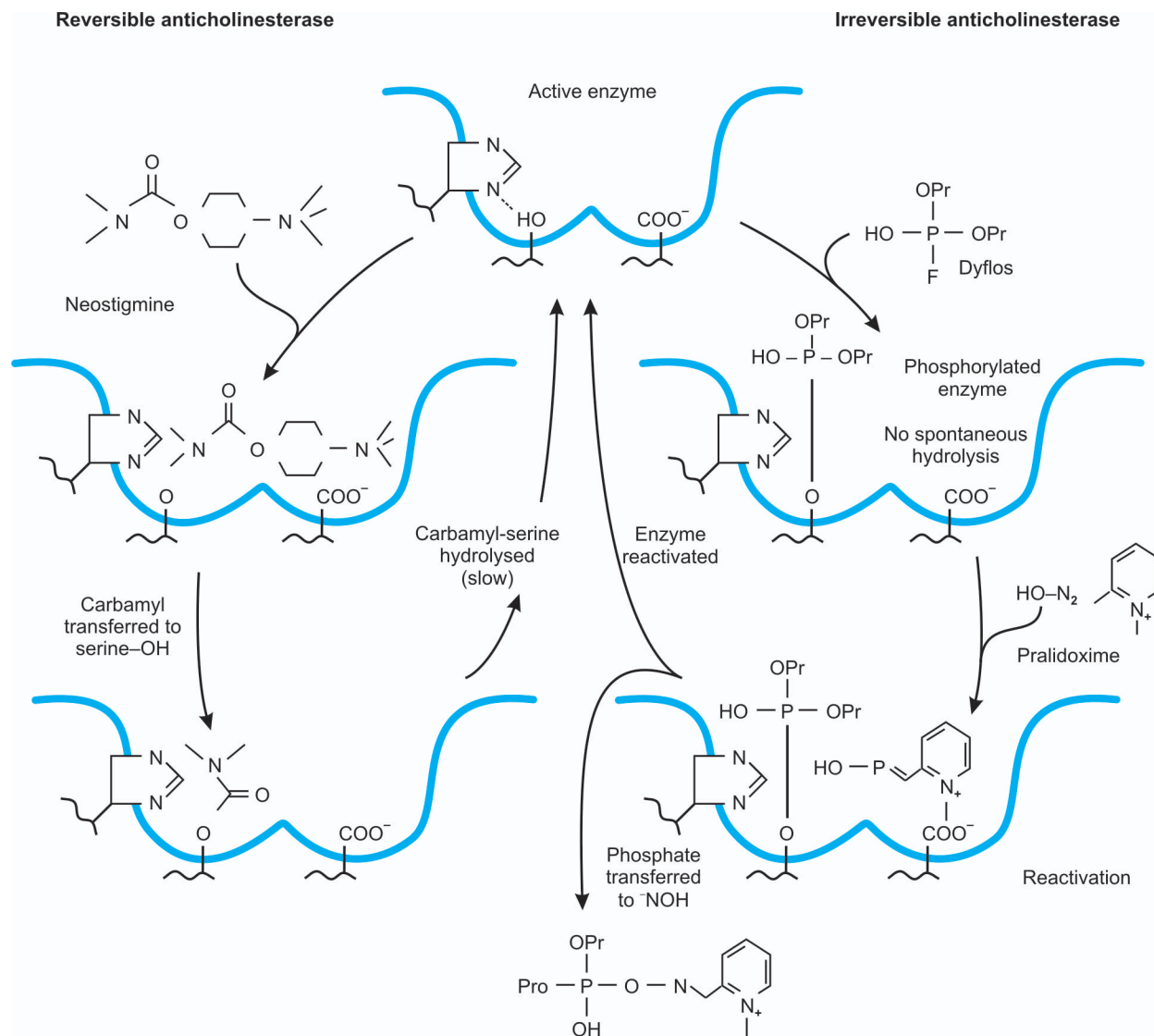


Fig. 2A.5.4: Action of anticholinesterase drugs including neostigmine (reversible) and dyflos (irreversible) anticholinesterases

- Corticosteroids - (prednisolone 30-60 mg/day)
- Azathioprine/Cyclosporine
- Plasmapheresis and Thymectomy can be planned.

- 3. Poisoning due to anticholinergic drugs:** Physostigmine is used in atropine poisoning and in toxicity due to other drugs with anticholinergic activity like phenothiazines, tricyclic antidepressants and antihistamines.
- 4. Curare poisoning:** Skeletal muscle paralysis caused by curare can be antagonised by Anti ChEs. Edrophonium is preferred for fast action.
- 5. Postoperative paralytic ileus and urinary retention:** Neostigmine may be useful.
- 6. Cobra bite:** Cobra venom, a neurotoxin causes skeletal muscle paralysis. Specific treatment is

antivenom. Intravenous edrophonium prevents respiratory paralysis.

Irreversible Anticholinesterases

- Organophosphorus compounds are powerful inhibitors of AChE enzyme; binding with the enzyme is permanent – by covalent bonds.
- Actions are similar to ACh as ACh accumulates in the tissues.
- Organophosphates are highly lipid soluble and hence are absorbed from all routes including intact skin.

Uses: *Glaucoma* – echothiophate eye drops are sometimes used in glaucoma.

Organophosphorus Poisoning

- AS organophosphates are used as agricultural and domestic insecticides, poisoning from them is quite common.
- Poisoning may be occupational – as while spraying insecticides, accidental or suicidal.

1. Preparations

- a. Di-isopropyl fluorophosphate (DFP) is an organophosphate compound, which forms a covalent bond between its phosphorus atom and the esteratic site of cholinesterase. The enzyme-inhibitor complex thus formed is irreversible. Its use is limited to the treatment of certain types of glaucoma.
- b. Echothiophate is a long-acting organophosphate cholinesterase inhibitor with pharmacological properties similar to those of DFP. Spontaneous regeneration of the phosphorylated enzyme can occur. Its major use is in the treatment of glaucoma.
- c. Parathion is an organophosphate anticholinesterase agent used as an insecticide. Its active form is paraoxon, a metabolite. Pharmacological and adverse effects are similar to those of DFP, (given below).

2. Adverse effects of DFP and other organophosphate (cholinesterase inhibitors) include:

- a. Miosis
- b. Increased bronchial secretions, profuse sweating, and increased lacrimation
- c. Anorexia, vomiting, and involuntary diarrhea
- d. Bradycardia

- e. Weakness of all skeletal muscles, especially those of respiration, after twitching and fasciculation.
- f. Anxiety, confusion, and convulsions, followed by vasomotor depression.

3. Reversal of cholinesterase inhibition: Pyridine-2-aldoxime methyl chloride (PAM, pralidoxime) reverses the effects of the organophosphate anticholinesterase agents. (Fig. 2A.5.4)

- a. It combines with and splits off the phosphorus from the esteratic site on cholinesterase in such a way that the enzyme is restored.
- b. With reactivation of the enzyme, the effects of acetylcholine begin to disappear.
- c. Treatment must be within hours, because the phosphorylated enzyme slowly changes to a form that cannot be reversed.

Treatment

1. If poisoning is through skin – remove clothing and wash the skin with soap and water; if consumed by oral route – gastric lavage should be done.
2. Maintain blood pressure and patent airway.
3. Drug of choice is atropine IV 2 mg every 10 minutes till pupil dilates.
4. Cholinesterase reactivators – **pralidoxime, obidoxime**. These compounds combine with cholinesterase organophosphate complex, release the binding and set free AChE enzyme. They should be given within a few hours (< 24 hrs) after poisoning, preferably immediately because the complex undergoes ageing and then the enzyme cannot be released.

Anticholinergic Drugs

Anticholinergic drugs are agents which block the effects of ACh on cholinergic receptors but conventionally antimuscarinic drugs are referred to as anticholinergic drugs. They are also called cholinergic blocking or parasympatholytic drugs.

- M (Muscarinic) receptor blocker or antagonist: **Anticholinergic drugs.**
- N_N (Nicotinic neuronal) receptor blocker or antagonist: **Ganglionic blocker.**
- N_M (Nicotinic muscular) receptor blocker or antagonist: **Neuromuscular blocker.**

Classification

Natural alkaloid: Atropine, Hyoscine (Scopolamine).

Semisynthetic: Homatropine, Homatropine methyl bromide, Hyoscine methyl bromide, Hyoscine butyl bromide, Ipratropium bromide, Tiotropium bromide.

Synthetic

- Mydriatic: Cyclopentolate, Tropicamide
- Anti-secretary:
 - Quarternary Ammonium compound: Oxyphenonium, Propantheline, Pymeprozate methyl bromide, Mepenzolate methyl bromide.
 - Tertiary Amine: Dicyclomine, Pirenzepine, Telenzapine

Anti-parkinsonian

- Benzhexol, Bextropine, Procyclidine, cycrimine.
- Tricyclic antidepressants, Antihistaminics and Phenothiazine.

Pharmacokinetics: Atropine and hyoscine are well-absorbed, cross the BBB and are metabolized in the liver.

PROTOTYPE DRUG: ATROPINE

Atropine is an alkaloid derived from the plant *Atropa belladonna* (deadly nightshade). The active component is the

racemic mixture dl-hyoscyamine, an ester compound of tropic acid and the organic base tropine. The levo isomers are much more active than dextro-isomer.

Mechanism of Action

- Atropine competes reversibly with acetylcholine at muscarinic receptors.
- At very high concentrations, it blocks acetylcholine at ganglionic synapses and motor nerve endings.
- Atropine antagonizes the action of acetylcholine in the CNS.

Actions: The actions of atropine and scopolamine are similar except that atropine is a CNS stimulant while scopolamine is a CNS depressant and causes sedation.

Effect on the heart

- The heart rate slows initially because there is stimulation of the cardio-inhibitory center in medulla.
- Tachycardia then follows with increased cardiac output and shortening of the P-R interval. Higher doses cause only tachycardia.

Effects on blood pressure

- Oral or intramuscular doses have little effect on blood pressure.
- With intravenous injection, total peripheral resistance increases.
- The increase in heart rate and cardiac output causes arterial pressure to increase.
- Atropine has a direct vasodilating effect on small blood vessels and histamine release ($\downarrow$ B.P.)

Effect on CNS

- In higher doses atropine stimulates the CNS resulting in restlessness, disorientation, hallucinations, delirium and coma.
- In contrast, scopolamine produces sedation and drowsiness. It also reduces vestibular excitation (antimotion property).

- Atropine possesses antitremor activity via a central antimuscarinic mechanism.

Secretions: Atropine reduces all secretions except milk. Lacrimal, salivary, nasopharyngeal, tracheobronchial and gastric secretions are decreased. Sweating is also reduced.

Smooth muscles: Atropine has following effects:

- In GIT—It ↓ tone and motility and relieves spasm which may result in constipation.
- In Biliary tract—smooth muscles are relaxed; biliary spasm is relieved.
- In Bronchi—Atropine causes bronchodilatation.
- In Urinary bladder—Atropine relaxes urinary bladder and may cause urinary retention.

Eye

- On local instillation, atropine produces mydriasis by blocking the muscarinic receptors in the sphincter pupillae.
- The ciliary muscle is paralysed resulting in cycloplegia or paralysis of accommodation.
- Because of mydriasis, the iris may block the (schlemms canal) drainage of aqueous humor; intraocular pressure increases and may precipitate glaucoma in some patients.
- It has mild local anesthetic action on cornea.

Body temperature: Atropine causes rise in body temperature at higher doses which is due to inhibition of sweating and stimulation of temperature regulating center in hypothalamus. Children are highly susceptible to atropine fever.

Uses of Atropine

- **As pre-anesthetic medication**
 - When administered 30 minutes before anesthesia, atropine reduces salivary and respiratory secretion. This will prevent the development of laryngospasm.
 - It also prevents bradycardia during surgery.
 - It's bronchodilator action is of additional value. Glycopyrrolate an atropine substitute, is most commonly used for this purpose.
- **As mydriatic and cycloplegic**
 - *Diagnostic:* for testing error of refraction and fundoscopic examination of the eye.
 - *Therapeutic:* To provide rest to the iritis, iridocyclitis and keratitis.
 - *Atropine substitutes*, i.e. homatropine, cyclopentolate and tropicamide are preferred over atropine.
 - Mydriatics are used alternately with miotics to break adhesions between the iris and the lens.

- **As antispasmodic:** In diarrhea and dysentery, atropine relieves abdominal pain.
 - In renal and biliary colic atropine is used with morphine.
 - In treatment of drug induced diarrhea.
 - Nocturnal enuresis in children and in paraplegia atropine reduces urinary frequency and urgency.
- **In organophosphorus poisoning:** Atropine is life saving in OP poisoning and is also useful in mushroom poisoning.
- **In bronchial asthma:** Atropine methonitrate and Ipratropium bromide by inhalational (aerosol) route are effective in the treatment of chronic obstructive pulmonary diseases (COPD), and asthmatic bronchitis.
- **In peptic ulcer:** Atropine derivatives are preferred over atropine.
- **For central action:**
 - *Parkinsonism:* Less effective than L - Dopa
 - *Motion sickness:* Hyoscine given 30 minutes before the journey prevents sickness. Transdermal hyoscine patches are available to be applied behind the ear for a prolonged action.
- Hyoscine can also be used during *labour* to produce sedation and amnesia (twilight sleep). Based on its same property it is also used **LIE DETECTOR AGENT**.
- Also used in the treatment of **dismenorrhea**.

Drug interactions: When anticholinergic drugs are given with other drugs that also have anticholinergic property like antihistaminics, phenothiazines, tricyclic antidepressants – side effects get added up.

Adverse effects of Belladonna Alkaloids (DHATURA):

These are common but not serious and include dry mouth, blurring of vision, dysphasia, dry skin, fever, constipation and difficulty in micturition. Skin rashes may appear. High doses cause palpitation, flushing, restlessness, delirium, hallucinations, psychosis, convulsions and coma. Poisoning is treated with IV physostigmine.

ATROPINE SUBSTITUTES

Belladonna alkaloids lack selectivity and exert a wide range of effects – producing many side effects. Hence several synthetic and semisynthetic derivatives with selective action were introduced.

Classification according to their uses

1. *Derivatives used on the eye*
 - Homatropine, Eucatropine, Cyclopentolate, Tropicamide
2. *Antispasmodics*
 - Atropine methonitrate Propantheline methantheline, Oxyphenonium, Glycopyrrolate

3. *Derivatives used in peptic ulcer*
 - Pirenzepine, Telenzepine
 4. *Derivatives used in bronchial asthma*
 - Ipratropium bromide
 5. *Antiparkinsonian drugs*
 - Benhexol, Benztropine, Trihexyphenidyl
- Mydriasis and cycloplegia produced by atropine lasts for 7-10 days. The derivatives have a shorter action (6-24 hours); some can selectively produce either mydriasis or cycloplegia and can be used in atropine intolerance.
 - Spasmolytics are used in colics, gastritis and peptic ulcer.
 - **Pirenzepine** – a selective M_1 -blocker inhibits gastric secretion at doses that does not affect other functions and has been tried in peptic ulcer.
 - When used in bronchial asthma, atropine thickens bronchial secretion and interferes with movement of cilia and thus favors formation of mucous plugs. **Ipratropium bromide** is a bronchodilator that does not affect mucociliary activity. When given as inhalation, it produces no systemic side effect. It is used in bronchial asthma and COPD.
 - **Benztropine, benhexol and trihexyphenidyl** are the centrally acting anticholinergics used in management of drug induced parkinsonism.



S E C T I O N

2B

Peripheral Nervous System

Skeletal Muscle Relaxants

DEFINITION

Skeletal muscle relaxants (SMR) are drugs that, reduces the muscle tone either by acting at the neuromuscular junction peripherally (neuromuscular blockers) or centrally in the cerebrospinal axis or directly on the contractile mechanism and relaxes the muscles.

CLASSIFICATION

1. Peripherally acting muscle relaxants: act at the Neuromuscular Junction

- *Competitive blockers (non-depolarizing)*: d-Tubocurarine, Gallamine, Pancuronium, Alcuronium, Atracurium, mivacurium, vecuronium.
- *Depolarizing blockers*: Succinylcholine, Decamethonium.

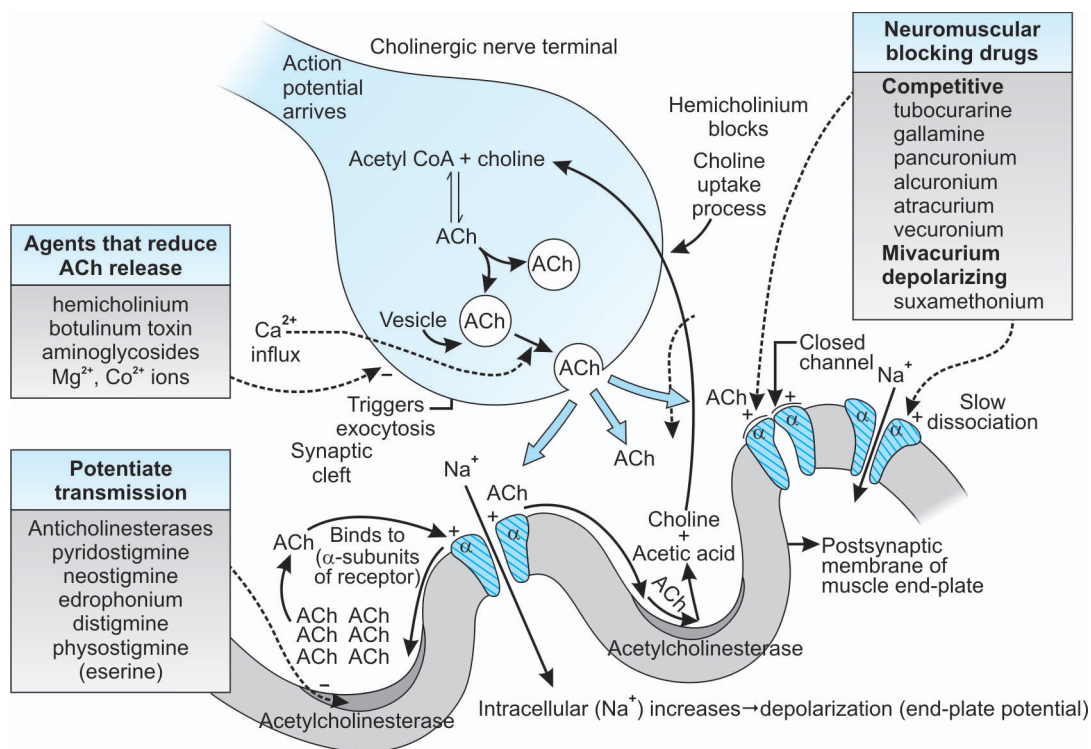


Fig. 2B.1.1: Drugs acting at the neuromuscular junction

2. **Drugs acting centrally:** Diazepam, Baclofen, Mephenesin.
3. **Drug acting directly on the muscle:** Dantrolene and Quinine.

PERIPHERALLY ACTING SKELETAL MUSCLE RELAXANTS

[NEUROMUSCULAR BLOCKERS]

Competitive Blockers

d-Tubocurarine

- i. Curare was used by the South American Indians as arrow poison for hunting wild animals as it paralyzed the animals.
- ii. On extensive research, the active principle from curare, d-tubocurarine (d-Tc) was identified. d-Tc is the dextrorotatory quaternary ammonium alkaloid obtained from the plant chondrodendron tomentosum and plants of the strychnos species.

Mechanism of action: d-Tc binds to nicotinic receptors on the motor end plate and it:

- Blocks the action of acetylcholine by competitive blockade. d-Tc slowly dissociates from the receptors and transmission is gradually restored, thus the action of d-Tc is reversible (Fig. 2B.1.1).

Pharmacological actions

Skeletal muscle: On parenteral administration, d-Tc initially causes muscular weakness followed by flaccid paralysis.

- i. Small muscles of the eyes and fingers are the first to be affected, followed by those of the limbs, neck and trunk. Later the intercostal muscles and finally the diaphragm are paralyzed and respiration stops.
- ii. Consciousness is not affected throughout.
- iii. Recovery occurs in the reverse order, i.e. the diaphragm is the first to recover. The effect lasts for 30-60 minutes.

Autonomic ganglia: In high doses d-Tc can block autonomic ganglia and adrenal medulla resulting in hypotension.

Histamine release: d-Tc can cause histamine release from tissues leading to bronchospasm, increased salivary, tracheobronchial and gastric secretions and also contribute to hypotension.

Other Systems

CVS: d-Tc caused significant fall in BP due to histamine release, ganglionic blockade and reduced venous return. HR may ↑ due to vagal blockade.

- d-Tc may cause postoperative paralytic ileus. It does not cross BBB but when applied locally on cortex it produces strychnine like effect.

Pharmacokinetics: d-Tc is a quaternary ammonium compound, hence not absorbed orally. It is given either IM or IV (Parenterally).

Dose and duration of action of competitive neuromuscular blockers:

Drug	Dose (mg/kg)	Duration (min)
d-Tubocurarine	0.2-0.4	35-60
Atracurium	0.3-0.6	20-35
Vecuronium	0.08-0.1	20-35
Mivacurium	0.07-0.1	12-18
Gallamine	1-1.5	35-60
Pancuronium	0.04-0.1	35-80
Doxacurium	0.03-0.08	90-120

Adverse Reaction

- i. Hypotension (Fall in blood pressure)
- ii. Respiratory paralysis and prolonged apnea
- iii. Flushing and bronchospasm due to histamine release by d-Tc. (May lead to precipitation of asthma)

Synthetic Competitive Blockers: Pancuronium, atracurium, vecuronium and gallamine have the following advantages over d-Tc.

- i. Less/no histamine release.
- ii. Do not block autonomic ganglia.
- iii. Spontaneous recovery takes place with most of these drugs.
- iv. Some are more potent than d-Tc.
 - d-Tc causes histamine release, ganglion blockade (resulting in hypotension) and its muscle relaxant effect needs to be reversed with drugs. Hence d-Tc is not used now. The synthetic compounds are preferred.
 - **Metocurine** causes histamine release less often than d-tubocurarine does, and atracurium is a less potent histamine releaser than either tubocurarine or metocurine.
 - Vecuronium causes no histamine release; thus, the risk of histamine-induced hypotension or bronchoconstriction is reduced.
 - Gallamine causes tachycardia and increased arterial pressure, the results of both vagolytic and tyramine-like effects.
 - Pancuronium also causes an increase in the heart rate and in arterial pressure, but to a lesser extent than gallamine does; the mechanism is not understood.
 - Pipercuronium can have a prolonged duration of action in patients with renal failure.

Depolarising Blockers: Succinylcholine (SCh) is a quaternary ammonium compound with the structure resembling two molecules of acetylcholine joined together.

Pharmacokinetics

1. SCh is rapidly hydrolyzed by pseudocholinesterase; hence it is short-acting.
2. Some people have an abnormal pseudocholinesterase, a hereditary defect;
3. SCh does not get metabolized and even the usual dose results in prolonged apnea. Artificial ventilation and fresh blood transfusion are needed.

Mechanism of action

1. The neuromuscular effects of SCh are like those of ACh.
2. SCh reacts with nicotinic receptors and depolarizes the skeletal muscle membrane. But unlike ACh, it is destroyed very slowly by pseudocholinesterase. Thus continued presence of the drug causes persistent depolarization resulting in flaccid paralysis. **This is phase I block.**
3. In high doses SCh produces a dual block—initial depolarizing block followed by non-depolarizing block. The membrane gets slowly repolarized but cannot be depolarized again. The mechanism is not clearly known. Ultimately desensitization of the receptor to ACh occurs and Phase II block develops.

Pharmacological actions

Skeletal muscle: Onset of action is very rapid, within 1 minute. Initial transient muscular fasciculations and twitchings, mostly in the chest and abdominal regions are followed by paralysis. It becomes maximum in 2 minutes and disappears in 5 minutes.

CVS: Hypotension and bradycardia may be seen initially as SCh is a partial agonist at nicotinic receptors, but it will be followed by ↑HR & BP due to stimulation of sympathetic ganglia.

Uses of Peripherally Acting Skeletal Muscle Relaxants:

1. Surgical adjuvant to anesthesia
 - i. For inducing skeletal muscle relaxation
 - ii. For facilitating endotracheal intubation
2. They are also useful in laryngoscopy, bronchoscopy, esophagoscopy and in orthopedic procedures like reduction of fractures.
3. *In electroconvulsive therapy:* They protect the patients from convulsions and trauma during ECT. (electroconvulsive therapy), specially SCh.
4. *In spastic disorders:* They are used to overcome the spasm of tetanus, athetosis and status epilepticus

specially repeated doses of competitive blocker, i.e. d-Tc.

5. In the diagnosis of myasthenia gravis (tubocurarine), although provocative tests of this sort are potentially hazardous.
6. Atracurium may be useful in patients with renal failure because it does not rely on the kidney for excretion.

Adverse reactions

- i. Postoperative muscle soreness due to initial fasciculations and cardiac arrhythmias may occur.
- ii. SCh may trigger the onset of malignant hyperthermia especially when used with halothane.

Drug interactions

- i. General anesthetics augment the action of SCh.
- ii. Anticholinesterases like neostigmine—reverse the action of competitive blockers.
- iii. Aminoglycosides and calcium channel blockers potentiate the action of skeletal muscle relaxants.
- iv. Sympathomimetics reduce competitive block.
- v. Propranolol, quinidine and diuretics enhance competitive block.
- vi. Steroid in higher dose reduces the block.

Reversal of Neuromuscular Blockade

1. Competitive neuromuscular blocker can be antagonized by cholinesterase inhibitors such as edrophonium, neostigmine or pyridostigmine.
2. No antagonists exist for depolarizing blockers.
 - i. Controlled ventilation is used until spontaneous recovery occurs.
 - ii. If an anticholinesterase is given, phase I block increases, but an anticholinesterase may reverse phase II block.

Factors influencing the action of neuromuscular blocking agents:

1. Serum cholinesterase is determined genetically; the normally transient effects of succinylcholine are greatly prolonged in an individual with deficient serum cholinesterase.
2. Because serum cholinesterase is synthesized in the liver, hepatic disease can double the duration of action of succinylcholine.
3. Echothiophate, an irreversible cholinesterase inhibitor used in the treatment of glaucoma, can significantly decrease cholinesterase activity and thereby increase the duration of action of succinylcholine.
4. Patients with myasthenia gravis are highly sensitive to competitive neuromuscular blocking agents, and phase II block occurs sooner than in normal individuals when depolarizing blockers are given.

5. Patients with Eaton-Lambert syndrome (small cell or oat cell carcinoma of the lung) have increased sensitivity to both competitive and depolarizing neuromuscular blockers.
6. Depolarizing neuromuscular blockers increase serum potassium; this is exacerbated in conditions that are associated with hyperkalemia, such as burns.
7. Aminoglycoside antibiotics and lincomycin exert a synergistic neuromuscular blockade when given with either competitive or depolarizing neuromuscular blocking agents; the mechanism is presynaptic.
8. All inhalation anesthetics increase the effects of neuromuscular blocking agents.

CENTRALLY ACTING MUSCLE RELAXANTS

These drugs act on higher centers and cause muscle relaxation without loss of consciousness. They also have sedative properties.

Mechanism of Action

Centrally acting muscle relaxants depress spinal polysynaptic reflexes.

Diazepam has useful anti-spastic activity. It facilitates GABA_A receptor transmission. It can be used in relieving muscle spasm of almost any origin including local muscle trauma.

Baclofen is an analog of the inhibitory neurotransmitter GABA. It is a [GABA_B] agonist depresses monosynaptic and polysynaptic reflexes in the spinal cord. It relieves painful spasms and may also improve bladder and bowel functions in patients with spinal lesions. *Side effects are drowsiness, weakness and ataxia.*

Mephenesin group of drugs are not preferred due to their side effects. A number of related drugs like carisoprodol, methocarbamol, chlorzoxazone are used in acute muscle spasm caused by local trauma. All of them also cause sedation.

Uses of Centrally Acting Muscle Relaxants

1. **Musculoskeletal disorders**—like muscle strains, sprains, myalgias, cervical root syndromes, herniated disk syndromes, low backache, dislocations, arthritis, fibrositis and bursitis all cause painful muscle spasms. Muscle relaxants are used with analgesics in these.
2. **Spastic neurological disorders**—like cerebral palsy, multiple sclerosis, poliomyelitis, hemiplegia and quadriplegia are treated with diazepam or baclofen.
3. **ECT:** [Electro convulsive Therapy]. Diazepam is given along with peripherally acting skeletal muscle relaxants.
4. **Tetanus:** Diazepam is given IV.

Directly Acting Muscle Relaxants

Dantrolene

1. Directly affects the skeletal muscle contractile mechanism.
2. It inhibits the muscle contraction by preventing the calcium release from the sarcoplasmic reticulum.
3. Adverse effects include drowsiness, dizziness, fatigue, diarrhea and rarely hepato-toxicity.

Uses

Dantrolene is used in spastic disorders and malignant hyperthermia.

Local Anesthetics

1. Local anesthetics are drugs/agents that act by blocking both sensory and motor nerve conduction to produce a temporary loss of sensation without a loss of consciousness. Their action is completely reversible.
2. Unlike general anesthetics, they normally do not cause central nervous system (CNS) depression.
3. Cocaine was the first agents to be isolated by Niemann in 1860. In spite of its addiction potential, cocaine was used for 30 years as a surface anesthetic. Later on other agents were discovered.

• **Compared to General anesthetics, Local anesthetic agents are:**

- Safer

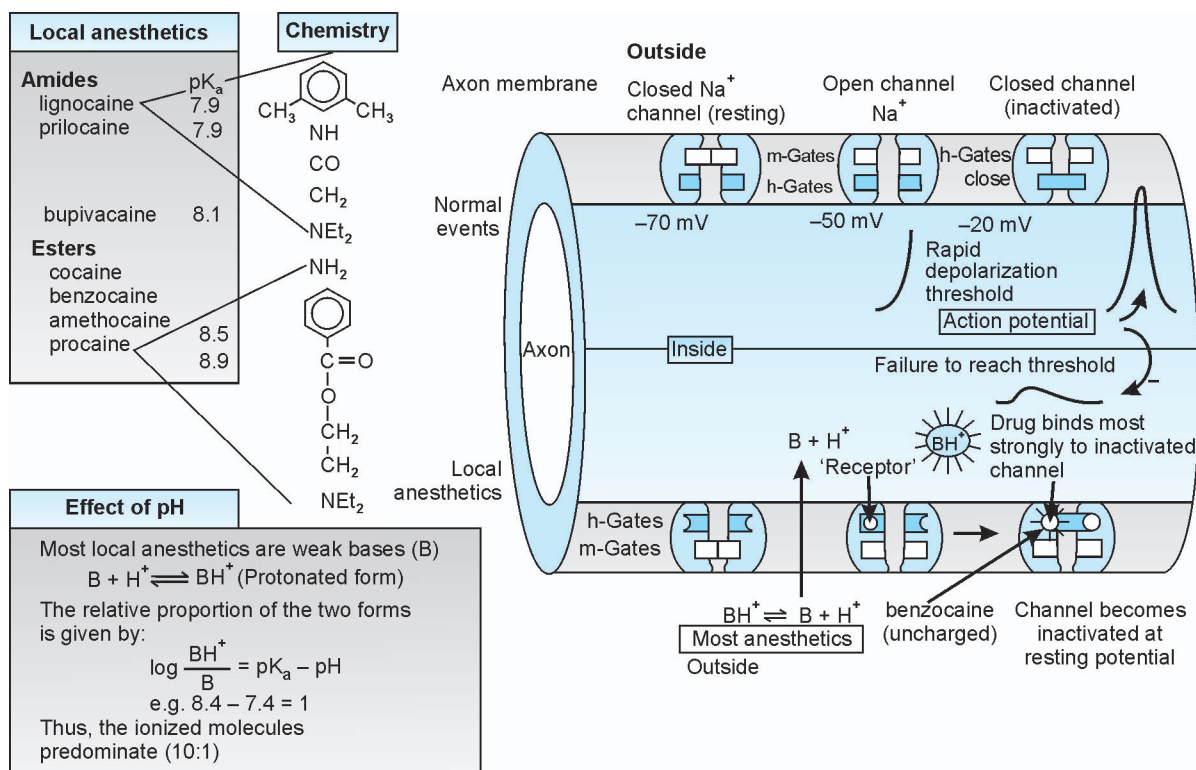
- There is no loss of consciousness
- Vital functions like heart-rate, respiratory rate, lung and liver functions are not disturbed.

• **Ideal local anesthetics are having:**

- Least adverse effect, i.e. should be non-irritant
- Short induction period.
- No tissue damage at the site of infiltration.
- Long-acting
- Least systemic toxicity.

Classification of local anesthetics (LAs)

- Surface anesthetics:** Lignocaine, Cocaine, Tetracaine, Benzocaine, Oxethazaine.



II. **Injectable**

1. Short-acting – Procaine, Chlorprocaine
2. Intermediate-acting – Lignocaine, Prilocaine
3. Long-acting – Tetracaine (amethocaine), Bupivacaine, Dibucaine (cinchocaine), Ropivacaine, Etidocaine
- Benzocaine, oxethazaine

Chemistry

1. **Structurally**, all local anesthetics consist of a hydrophilic amino group linked through a connecting group to a lipophilic aromatic residue. The greater the length of the connecting and amino groups, the greater the potency and the toxicity of the local anesthetic. Depending on the linkage, LAs can be classified as:

Ester linked: Cocaine, Procaine, Tetracaine, Benzocaine, Chlorprocaine.

Amide linked: Lignocaine (Lidocaine), Mepivacaine, Bupivacaine, Etidocaine, Prilocaine, Ropivacaine and Dibucaine.



2. **Local anesthetics** are weak bases and, thus, are usually water-insoluble. The drug may be dispensed as a crystal but usually is prepared as an acidic salt solution, which is highly water-soluble and stable.
3. At tissue pH, depending on the pK_a of the agent, the drug exists as either an uncharged tertiary or secondary amino base form or a positively charged ammonium cation. The former state is lipophilic and crosses connective tissue and enters nerve cells; the cation is thought to block the generation of action potentials via a membrane-receptor complex.

Mechanism of action

1. Local anesthetics slows/blocks the propagation of nerve impulses by preventing the generation and the conduction of nerve impulses. The primary mechanism of action is blockade of voltage-gated sodium channels as shown in Fig. 2B.2.1.
 - a. The increased threshold for electrical excitability results in a complete block of conduction.
 - b. Local anesthetics specifically block nerve conduction by interfering with cell membrane permeability to sodium, particularly voltage-dependent Na^+ channels. Two theories may explain the mechanism of interference with membrane permeability.
 - i. The specific receptor theory postulates that the local anesthetic displaces Ca^{2+} from a site near the Na^+ channel and then blocks the adjacent Na^+ channels.
 - ii. The membrane expansion theory hypothesizes that local anesthetics, because of their lipophilic properties, incorporate into the cell membrane, preventing the opening of pores and, thus, interfering with the passage of electrolytes.

2. A differential sensitivity of nerve fibers to local anesthetics has been identified and characterized.

- a. The smallest unmyelinated fibers, which conduct impulses for pain, temperature, touch, pressure vibration sensations and autonomic activity, (conduct slowly) are the first to be blocked by local anesthetics. Non-myelinated fibres are blocked more readily than the myelinated.
- b. Critical length is the exposure time required by an anesthetic in order for it to exert its action; smaller nerve fibers have a proportionally smaller critical length.
- c. Addition of a vasoconstrictor like adrenaline (1:1,00,000 to 1:2,00,000) or phenylephrine (1:20,000):
 - i. Prolongs the duration of a action of LAs by slowing the rate of absorption from the *site of administration*.
 - ii. Reduces systemic toxicity of LAs since the absorption rate is reduced and as it gets absorbed, it gets metabolised.

Systemic actions: LAs interfere with the function of all organs in which conduction or transmission of impulses occur. Thus autonomic ganglia, central nervous system, neuromuscular junction and all muscles are affected. Depending on the concentration attained in the plasma, any LA can produce systemic effects.

CNS

- LAS depress the cortical inhibitory pathway thereby allowing unopposed activity of excitatory components.
- This loss of inhibition is manifested as restlessness, tremors and may proceed to convulsions. This central stimulation is followed by generalized CNS depression and death may result from respiratory failure.

Cardiovascular system

- The primary site of action is the myocardium—lignocaine decreases excitability, conduction rate, and force of contraction (quinidine like effects).
- They also cause arteriolar dilatation. Since procaine is short-acting, procainamide is used as an antiarrhythmic agent. Bupivacaine is more cardiotoxic than other LAs.

Smooth muscle

- LAs depress contractions in the intact bowel. They also relax vascular and bronchial smooth muscles.

Pharmacokinetics

1. Local anesthetics are rapidly absorbed from the mucus membranes and abraded skin.
2. Rate of absorption is dependent on the vascularity of the area.
3. Vaso-constriction decreases the absorption.
4. Toxicity depends on the balance between absorption and metabolism, i.e. if it get absorbed, then toxicity is less. Binding to tissues decreases the concentration in systemic circulation and thereby toxicity.
5. Ester-linked LAs are rapidly hydrolyzed by plasma pseudocholinesterase and in the liver.
6. Amide linked LAs are metabolized by the liver microsomes by dealkylation and hydrolysis and are not effective orally (as antiarrhythmics). They undergo extensive first pass metabolism.

Adverse Effects

1. **Hypersensitivity reaction:** skin rashes, dermatitis, asthma or rarely anaphylaxis. These reactions are more common with ester type of drugs while with amides, allergy is rare. Ester type LA are metabolized to PABA

derivatives. These are responsible for allergic reactions however, allergy is also most often due to the preservative methylparaben. Preparations that do not contain this preservative are now available.

2. **Local irritation:** Like inflammation, thrombophlebitis can be seen with bupivacaine like drug. Wound healing may be delayed.
3. **Cental nervous system:** Dizziness, auditory and visual disturbances, mental confusion, disorientation, anxiety, muscle tremor, convulsions and respiratory failure can result from large doses. Intravenous diazepam controls convulsions. Infact, it can be prevented by preanesthetic medication of diazepam (1-2 mg/kg).
4. **Cardiovascular system:** Hypotension, bradycardia, arrhythmias may be encountered. Rarely cardiac arrest can occur.

Individual Agents (Table 2B.2.1)**Cocaine**

Chemistry: It is an ester of benzoic acid.

Pharmacokinetics

- i. Cocaine is quickly degraded by plasma esterases and has a half-life of approximately 1 hour.
- ii. Cocaine is metabolized in the blood by ester hydrolysis using pseudocholinesterase.

Table 2B.2.1: Local anesthetics: preparations and therapeutic uses

Agents	Preparations	Therapeutic uses
Cocaine	4%-10% concentration, solution	Topical anesthesia of nose, pharynx, and tracheobronchial tree; use limited by abuse potential
Procaine	1%-2% solution	Nerve block, infiltrative anesthesia
	5%-20% solution	Spinal anesthesia
Tetracaine	10% dextrose solution	Spinal anesthesia
	2% solution	Topical anesthesia of mucous membranes
Lidocaine	1%-2% solution, ointment,	Topical anesthesia of mucous membranes; jelly, or cream
	0.5% solution	nerve block anesthesia
	<5% solution	Infiltrative anesthesia
Prilocaine	1%-3% solution	Spinal anesthesia
Etidocaine	0.5%-1.5 solution	Infiltrative, regional, and spinal anesthesia
Mepivacaine	1%-4% solution	Infiltrative, regional, and epidural anesthesia
Bupivacaine	0.25%-0.75% solution	Infiltrative and regional nerve block anesthesia
Dibucaine	0.2% solution	Regional nerve block anesthesia
Benzocaine	1-2% solution	Topical anesthesia of mucous membranes.
Oxethazaine	0.2% suspension	Topical anesthesia
Ropivacaine	2-10% Inj.	Topical anesthesia (used in peptic ulcer)
		Infiltration, nerve block, spinal, epidural anesthesia

Pharmacological effects: In addition to local anesthetic activity, the spectrum of activity of cocaine includes the following:

1. **CNS effects**
 - a. Cocaine initially produces CNS stimulation (euphoria) and sometimes dysphoria.
 - b. The initial effect is followed by post-stimulatory depression.
2. **CVS effects**
 - a. Cocaine blocks the uptake of catecholamines at adrenergic nerve terminals.
 - b. This causes sympathetically mediated tachycardia and vasoconstriction, leading to hypertension. (The vasoconstriction also decreases intraoperative mucous membrane bleeding).

Adverse effects

1. Tolerance, abuse liability and poisoning can occur with cocaine overuse.
2. Hyperpyrexia
3. Anorexia

Procaine: Chemistry: It is an ester of diethylaminoethanol and paraaminobenzoic acid (PABA).

Pharmacokinetics

1. Procaine is well absorbed following parenteral administration and is rapidly metabolized by pseudocholinesterase. It has a short duration of action.
2. The metabolic product of procaine hydrolysis is PABA, which inhibits the action of sulfonamides.
3. The drug lacks topical activity.
4. Procaine administration causes minimal systemic toxicity and no local irritation.

Preparations and therapeutic uses: Procaine hydrochloride is available with and without epinephrine. Epinephrine, a vasoconstrictor, decreases the rate of anesthetic absorption in the bloodstream and so approximately doubles the duration of anesthesia produced by a given dose.

Tetracaine

Chemistry: It is an ester and derivative of PABA.

Pharmacokinetics

- i. Tetracaine is approximately 10 times more potent (and more toxic) than procaine.
- ii. Its onset of action is approximately 5 minutes, and its duration of action is between 2-3 hrs.

Preparations and therapeutic uses

- i. Tetracaine hydrochloride is a commonly used local anesthetic for spinal anesthesia and, in this context, usually it combined with 10% dextrose to increase the specific gravity so that the solution is heavier than cerebrospinal fluid.

- ii. A 2% solution is used topically on mucous membranes.

Lidocaine

Chemistry.: It is an amide local anesthetic and an acetanilid derivative.

Pharmacokinetics: Lidocaine is rapidly absorbed after parenteral administration and is metabolized in the liver by microsomal mixed-function oxidases, (engymes).

Pharmacological effects include:

- i. Rapid onset of anesthesia.
- ii. Minimal local irritation.
- iii. A greater potency and longer duration of action than procaine
- iv. Moderate topical activity.

Preparations and therapeutic uses: Lidocaine hydrochloride can be administered with or without epinephrine. The major clinical uses of lidocaine are as a local anesthetic and as an antiarrhythmic agent.

XYLOCAINE 4% topical solution, 2% jelly, 5% ointment, 1% and 2% injection. 5% for spinal anesthesia.

Prilocaine

Chemistry: It is an amide local anaesthetic.

Pharmacokinetics: The onset and duration of action of prilocaine are slightly longer than those of lidocaine.

Adverse effects: The major disadvantage of prilocaine is the production of methaemoglobinemia and a shift to the left of the oxygen-dissociation curve for hemoglobin.

Etidocaine

Pharmacokinetics: Etidocaine is similar to lidocaine except for its greater potency and longer duration of action.

Preparations and therapeutic uses

- i. Etidocaine is used clinically in epidural, infiltrative, and regional anesthesia. The drug usually blocks motor fibers before sensory fibers.
- ii. Etidocaine hydrochloride is available both with or without epinephrine.

Mepivacaine: Chemistry : Like lidocaine mepivacaine is an amide-type local anesthetic.

Pharmacokinetics: Mepivacaine is similar to lidocaine; however, it does not have antiarrhythmic activity.

In onset of action, mepivacaine is more rapid than lidocaine, and its duration of action is about 20% longer.

Preparations and therapeutic uses

Epinephrine is rarely used with this drug. Uses are more or less similar to lidocaine.

Bupivacaine

Chemistry: It is an amide local anesthetic, bupivacaine is structurally similar to mepivacaine.

Pharmacokinetics: Bupivacaine is more potent and has a longer duration of action than mepivacaine, lasting for more than 24 hours in some situations, possibly as a result of increased tissue binding. The onset of action is slower than that of mepivacaine.

Preparation and therapeutic uses

- Popular in obstetric uses.
- For postoperative pain relief.

Adverse effects: Toxicities are similar to that of tetracaine; however, cardiac arrest has been reported in association with a 0.75% solution of bupivacaine used for obstetric epidural anesthesia.

Dibucaine

Chemistry: It is a substituted amide and a quinoline derivative.

Pharmacokinetics

- i. Dibucaine is a potent anesthetic with a long duration of action.
- ii. It has a high systemic toxicity and is used only as a topical anesthetic.

Local anesthetics used only on the eye

1. **Benoxinate HCl:** Within 60 seconds of administration it produces corneal anesthesia enough to perform tonometry.
2. **Proparacaine HCl:** Produces little or no initial irritation—0.5% ophthalmic solution is used.

Local anesthetics used on the skin and mucous membranes:

- i. LAs used on the skin and mucous membranes are **dibucaine hydrochloride and pramoxine hydrochloride**.
- ii. These drugs are effective when used topically in the symptomatic relief of anal and genital pruritus, poison ivy rashes, acute and chronic dermatoses.
- iii. Dibucaine is the most potent, most toxic and longest-acting LA. It is available as cream and ointment.

Poorly soluble anesthetic: These are too slowly absorbed to be toxic. They can be applied to wounds directly and ulcerated surfaces as they produce sustained anesthetic effect, e.g. benzocaine.

Adverse systemic effects of local anesthetics: It results from absorption of toxic amounts of these agents into the bloodstream. Adding epinephrine to the optimal

concentration of a local anesthetic reduces the rate of systemic absorption, thereby decreasing systemic toxicity.

1. **Seizures:** They are result of absorption of the local anesthetic and stimulation of the CNS. They are the most serious adverse effect. Convulsions, if they occur, are treated with basic supportive measures, including ventilation and oxygenation, and with intravenous diazepam.
2. **Respiratory failure** secondary to CNS depression is a late stage of intoxication. Hypotension and ischemia of the respiratory center results in respiratory failure. Due to paralysis of the abdominal muscles, cough reflex is less effective resulting in stasis of respiratory secretions respiratory infections.
3. **A quinidine-like effect** on the myocardium can be produced by local anesthetics.
4. **Hypotension and bradycardia** is a late effect that can occur as the result of myocardial depression and peripheral arterial vasodilation; affected patients are treated with appropriate parenteral vasopressor agents.
5. **Allergic reactions** to local anesthetic agents rarely occur.
6. Injection of LAs are painful, wound healing may be delayed.

Uses of Local Anesthetics

Depending on the site and technique of administration, LA can be:

Surface anesthesia

- i. Anesthesia of mucous membrane of the eye, nose, mouth, tracheobronchial tree, esophagus and genitourinary tract can be produced by direct application of the anesthetic solution. Anesthesia is entirely superficial and does not extend to submucosal structures.
- ii. Tetracaine 2%, lignocaine 2-10% are most often used.
- iii. Phenylephrine (but not adrenaline) produces vasoconstriction on topical application and prolongs duration of action.
- iv. LAs are absorbed from mucous membranes and may result in systemic toxicity. Patient should be cautioned to expectorate the excess solution to avoid excess absorption.
- v. Local anesthetics can also be used on abraded skin.
- vi. Surface anesthesia is useful in the eye for tonometry, minor surgery, nasal lesions, stomatitis, sore throat, tonsillectomy, endoscopies, intubation, gastric ulcer, burns and proctoscopy.

Infiltration anesthesia

- i. Injection of a local anesthetic solution directly into the tissue can be
 - a. Superficial—only into the skin, or

- b. Into deeper structures including intra-abdominal organs. Duration can be doubled by adrenaline (1:2,00,000). Adrenaline should not be used
 - around end arteries to avoid necrosis, and
 - intracutaneously to avoid sloughing.
- ii. Advantage by using infiltration anesthesia, it is possible to provide anesthesia without disruption of normal bodily functions.
- iii. Drugs used are lignocaine, procaine, bupivacaine.
- iv. Disadvantage in major surgeries—systemic toxicity due to local anesthetic is likely as large amounts of the anesthetic is required for such procedures.
- v. Uses for minor procedures like incisions, drainage of an abscess, excision, etc.

Field block:

- i. Subcutaneous injection of a LA solution proximal to the site to be anesthetised, interrupts nerve transmission in the region distal to the injection.
- ii. Sites such as forearm, scalp, anterior abdominal wall and lower extremity are used for field block. Knowledge of the relevant neuroanatomy is essential.
- iii. Advantage: Lesser dose can be used to provide a greater area of anesthesia.

Nerve block: Injection of a solution of a LA around individual peripheral nerves or nerve plexuses produces larger areas of anesthesia with a smaller amount of the drug than the above techniques.

Nerve block anesthesia is useful for:

- i. Sensory cranial nerve blocks.
- ii. Blocking of brachial plexus for procedures on arm (distal to deltoid).
- iii. Radial and ulnar nerve block at the elbow.
- iv. Facial and lingual nerve blocks for procedures on face and tongue.
- v. Intercostal nerve blocks to anesthetise anterior abdominal wall.
- vi. Cervical plexus block for surgery of the neck.
- vii. Sciatic and femoral nerve blocks for surgeries distal to the knee.
- viii. Blocks of nerves at wrist and ankle.
- ix. Inferior alveolar nerve blocks for extraction of lower jaw teeth.
- x. Duration depends on lipid solubility and protein binding. Anesthesia lasts longer than by field block or infiltration techniques. Nerve blocks are done for tooth extraction, operations on the eye, and in neuralgias.

Spinal anesthesia (SA)

- i. Local anesthetic solution is injected into the subarachnoid space between L2-3 or L3-4 below the lower end of the spinal cord. The drug acts on nerve roots.

- ii. Lower abdomen and lower limbs are anesthetized and paralyzed. The level of anesthesia can be altered by the volume of injection, specific gravity of the solution and posture of the patient.
- iii. Generally a hyperbaric solution (in 10% glucose) is injected. Iso and hypobaric solutions can also be given.
- iv. Level of sympathetic block produced is 2 segments higher and motor paralysis 2 segments lower than sensory or cutaneous anesthesia.
- v. Duration depends on the concentration, dose and the drug itself.
- vi. **Advantages:** Safer, affords good analgesia and muscle relaxation and there is no loss of consciousness. In cardiac, pulmonary and renal diseases, SA can be employed without much complication.
- vii. **Uses:** Surgical procedures on the lower limb, pelvis, lower abdomen, obstetric procedures, caesarean section and other operations are done on spinal anesthesia.

Complications of spinal anesthesia

1. Cauda equina syndrome is uncommon in which control over bladder and bowel sphincters is lost because of damage to nerve roots.
2. Sepsis : resulting in meningitis.
3. Headache due to seepage of CSF, can be treated with analgesics.
4. Nausea and vomiting: premedication can be given to prevent this.
5. Respiratory paralysis and
6. Hypotension due to blockade of sympathetic outflow.

Contraindication to spinal anesthesia

- Low circulating Vol. (hypotension)
- Abnormal vertebral column, i.e. kyphosis, scoliosis.
- Infection at injection site
- Infant and Children
- Non co-operative or schizophrenic patients.

Epidural anesthesia

- i. LA is injected into the spinal extradural space. It acts on nerve roots while small amounts diffuse into subarachnoid space.
- ii. It is technically more difficult and comparatively larger volumes are needed.
- iii. After repeated injections tachyphylaxis may develop.
- iv. Injection is made in:
 - a. Thoracic region.
 - b. Lumbar region.
 - c. Caudal region depending upon the site of requirement of anesthesia for surgical procedures.

Advantages

1. Difference between sensory and motor blockade in 4-5 segments, with higher sensory blockade. This is useful for obstetric analgesia, as the mother has painless labor and can still cooperate in the process of labor and is conscious throughout.
2. As there is no risk of injecting into Sub-arachinoidal space, there are no chances of infection.

Intravenous regional anesthesia

- i. This type of anesthesia is useful for rapid anesthetization of an extremity. A rubber bandage is used to force

blood out of the limb (veins) and a tourniquet is applied to prevent the re-entry of the blood.

- ii. A dilute solution of the local anesthetic is then injected intravenously. It diffuses into extravascular tissues.
- iii. Onset of anesthesia is in 2 minutes. Because of the pain produced by the tourniquet, this type of anesthesia is used for procedures lasting less than one hour.
- iv. About 25% of the drug enters into the systemic circulation. This type of anesthesia is commonly used on the upper limbs though it can also be used on the legs and the thighs.



S E C T I O N

3

Autacoids

Autacoids: Histamine and Antihistaminics

The word autacoids is derived from Greek: autos – self, akos – healing substance/remedy.

Definition

1. Autacoids are substances formed in various tissues, have complex physiological and pathological actions and act locally at the site of synthesis.
2. They have a brief action and are destroyed locally. Hence they are called local hormones and differ from true hormones which are produced by specific cells and reach their target tissues through circulation.
3. They are involved in a number of physiological and pathological processes.

Classification of autacoids is shown in Table 3.1.1.

Table 3.1.1: Classification of autacoids

1. Amine autacoids

- i. Histamine
- ii. 5-Hydroxy-tryptamine (Serotonin).

2. Peptide autacoids

- i. Plasma kinins: Bradykinin/Kallidian
- ii. Angiotensin.

3. Lipid derivative autacoids

- i. Prostaglandin (PGn)
- ii. Leukotriens (LT)
- iii. Platelet activating factor (PAF).

4. Others

- i. Vassopressin (ADH), Cytokines (IL, TNF-alfa, etc.)
- ii. Atrial natriuretic peptide (ANP)
- iii. Endothelin/EDRF
- iv. VIP, Substance P, Neuropeptide Y, etc.

HISTAMINE AND ANTIHISTAMINICS

Histamine

Histamine: (tissue amine) (Histo = tissue)

1. It is a biogenic amine formed in many tissues. It is also found in the venom of bees, wasp and other stinging secretions.

2. Dale established relation between action of histamine and allergic reactions.
3. First synthesized in 1907.

Synthesis, storage, distribution and degradation

- Histamine is formed by the decarboxylation of the amino acid (histidine) (Fig. 3.1.1).
- Tissue rich in histamine are: lungs, skin, intestine, liver and placenta. It is stored in the granules of the mast cells and basophiles in an inactive form.
- Non-mast cell histamine found in brain (serves as a neurotransmitter), epidermis and in growing region.

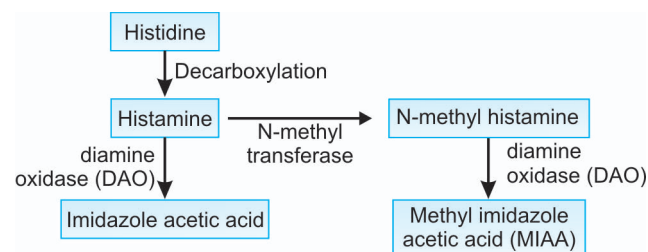


Fig. 3.1.1: Formation of histamine

- Degranulation of the mast cells (Fig. 3.1.2) release histamine which is quickly degraded by deamination and methylation.

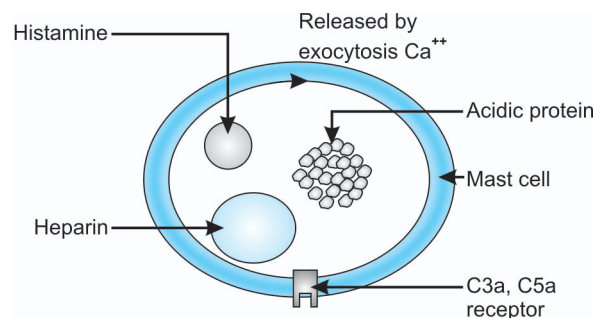


Fig. 3.1.2: Mast cell

Mechanism of Action

- Histamine produces its effects by acting on the histamine receptors. Three subtypes are known.
 - H_1 : present in lungs, gut, blood vessels, nerve endings and brain.
 - H_2 : stomach (gastric glands), heart, blood vessels and brain.
 - H_3 : CNS.

Actions

CVS: Histamine dilates small blood vessels resulting in hypotension accompanied by reflex tachycardia. But cerebral blood vessels dilate producing severe throbbing headache.

Triple response: Intradermal injection of histamine elicits triple response comprising of:

- Red spot:** at the site (flush): due to local capillary dilation.
- Flare:** redness surrounding the 'flush' due to arteriolar dilatation.
- Wheal:** local edema due to the escape of fluid from the capillaries.
This response is accompanied by pain and itching.

Smooth muscle: Histamine causes contraction of the non-vascular smooth muscles. Thus bronchospasm and increased intestinal motility are produced. Actions on other visceral smooth muscles like uterus are insignificant in human.

Glands: Histamine is a powerful stimulant of the gastric acid secretion (acts through H_2 receptors). It also stimulates pepsin and intrinsic factor secretion.

CNS: It does not cross BBB

- Direct injection in brain produces hypertension and behavioral arousal.
- Histamine functions as a neurotransmitter in the CNS.

Skin

Sensory Nerve endings :

- Histamine stimulates sensory nerve endings causing pain and itching.
- Intradermal injection of histamine produces triple response.

Adverse reactions: They include: hypotension, flushing, tachycardia, headache, wheals, bronchospasm and diarrhea.

Uses: Histamine is of no therapeutic value. It is occasionally used in some diagnostic tests like.

- Testing gastric acid secretion :** To test the acid secreting ability of the stomach. But now pentagastrin is preferred for this purpose.
- Diagnosis of pheochromocytoma :** Histamine releases catecholamines and rises BP – now not used.
- Testing pulmonary functions :** To test bronchial hyperactivity.

Histamine substitutes: Betazole is a H_2 agonist and can be used in gastric function tests. Betahistine is a H_1 agonist used to control vertigo in Meniere's disease.

Antihistaminics

- Histamine antagonists can be H_1 receptor blockers and H_2 receptor blockers.
- Drugs that competitively block H_1 histamine receptors are conventionally called the 'antihistaminics'. H_2 blockers are used in the treatment of peptic ulcer.
- Classification of H_1 receptor blockers are shown in Table 3.1.2.

Table 3.1.2: Classification of H_1 blockers

Sedative	Diphenhydramine, Dimenhydrinate, Promethazine.
Less sedative	Pheniramine, Chlorpheniramine, Cyclizine, Meclizine, Buclizine, Mepyramine, Tripeleminamine.
Newer non-sedative (II generation agents)	Terfenadine, Astemizole, Loratidine, Cetirizine.

Actions

- Blockade of histamine actions:** H_1 receptor antagonists block the actions of histamine on H_1 receptors. They block the histamine induced effects on smooth muscles of the gut, bronchi, blood vessels and triple response.
- Antimotion sickness effects:** Several antihistamines prevent motion sickness and vomiting due to other labyrinthine disturbances. Some of them also control vomiting of pregnancy.
- Anticholinergic actions:** Many of the H_1 blockers have anticholinergic property.
- Sedation:** Antihistamines cause CNS depression; sedation, dizziness, inability to concentrate and disturbances of coordination are common. Alcohol and other CNS depressants potentiate this action. Some patients may experience CNS stimulation resulting in tremor, restlessness and insomnia.
- Antiparkinsonian effects:** Some of them suppress tremors, rigidity and sialorrhea probably due to their anticholinergic properties.
- Other actions:** Antihistamines also have local anesthetic effects in high doses. Some of them also block α_1 adrenergic and 5-HT receptors.

Pharmacokinetics

- Antihistaminics are well-absorbed.
- They are widely distributed in the body.
- Histamine is metabolised in the liver and excreted in the urine.
- Dose and route of administration see in Table 3.1.3.

Table 3.1.3: Dose and preparations of some antihistaminics

Antihistaminics	Dose and route	Trade name
Diphenhydramine HCl	25-50 mg oral, IM	BENADRYL Cap, Syr
Dimenhydrinate	25-50 mg oral, IM	DRAMAMINE Tab, Syr Inj
Promethazine	25-50 mg oral, IM	PHENERGAN Tab, Syr, Inj
Promethazine chlortheophyllinate	25-75 mg oral, IM	AVOMINE Tab
Pheniramine maleate	25-50 mg oral, IM	AVIL Tab, Syr, Inj
Chlorpheniramine	4-20 mg oral, IM	ZEET Tab, Syr, Inj
Cyclizine HCl	50 mg oral	MAREZINE Tab
Meclizine HCl	25-50 mg oral	ANCOLAN Tab
Bucizine	25-50 mg oral	LONGIFENE Tab, Syr
Cinnarizine	25-50 mg oral	STUGERON Tab
Nonsedative (II generation) antihistaminics		
Terfenadine	60 mg oral	TREXYL Tab, Syr
Astemizole	10 mg oral	ASTELONG, Tab, Syr
Loratadine	10 mg oral	LORFAST, Tab, Syr
Cetirizine	10 mg oral	ALERID, Tab, Syr

Adverse reactions: They are mild and on continue use tolerance develops:

- Sedation, dizziness, motor in coordination, inability to concentrate making driving dangerous (while on antihistaminics).
- Anticholinergic effects like dryness of mouth, blurred vision, constipation and urinary retention may be troublesome.
- Epigastric pain and headache can also occur.
- Many of them are teratogenic (toxic to fetus).

Newer non-sedative antihistaminics

- They are also called IInd generation antihistaminics and have the following advantages over classical antihistaminics:
 - No sedation because they poorly cross the blood-brain barrier.
 - No anticholinergic side effects as they are pure H₁ blockers and do not block cholinergic receptors.
 - Some of them like astemizole are long-acting.
- However, the therapeutic indications of these agents are limited to allergic disorders like allergic rhinitis and chronic urticaria. They are more expensive.
- Terfenadine can very rarely cause fatal ventricular arrhythmias; erythromycin and ketoconazole potentiate this cardiotoxicity.

Uses

- **Allergic reactions:** Antihistaminics are useful for the prevention and treatment of symptoms of allergic

reactions. They are effective in allergic rhinitis, conjunctivitis, hayfever, urticaria, pruritus, some allergic skin rashes and pollinosis.

- Though they prevent bronchospasm induced by histamine, antihistaminics are not useful in bronchial asthma as many other mediators are also involved in the pathogenesis of bronchial asthma. Moreover, antihistaminics render the respiratory secretions more thick making it difficult to remove it and through it out.

- **Common cold:** Antihistaminics reduce rhinorrhea and afford symptomatic relief in common cold.
- **Cough:** Due to postnasal drip can be controlled by antihistaminics like diphenhydramine.
- **Motion sickness:** Given 30-60 minutes before journey, antihistaminics prevent motion sickness. They are also useful in treating vertigo of Meniere's disease and other vestibular disturbances. Cinnarizine is preferred.
- **Antiemetic:** Promethazine is used to prevent drug induced and postoperative vomiting. It has also been used in 'morning sickness'.
- **Preanesthetic medication:** For the sedative, anticholinergic and antiemetic properties, promethazine has been used as preanesthetic medication.
- **Parkinsonism:** Some of them are useful in drug induced parkinsonism due to their anticholinergic action.
- **Hypnotic:** The sedative antihistaminics are sometimes used to induce sleep. Hydroxyzine has been used as an anxiolytic.

Eicosanoids and Platelet Activating Factor

Eicosanoids are 20-carbon (*eicosa* referring to the 20-C atoms and anoids means 4 double bond).

- They are not found preformed in the tissues.
- They are most important mediators of inflammatory reactions.
- They are unsaturated fatty acids derived mainly from arachidonic acid in the cell walls. The principal eicosanoids are the prostaglandins (PGs), the thromboxanes (TXs), and the leukotrienes (LTs).

Principal Eicosanoids and Prostanoids

Prostaglandins (PGs)	Prostaglandins (PGs)
Thromboxane (TXs)	Thromboxanes (TXs)
Prostacycline PGI_2	
Leukotrienes LTs	

BIOSYNTHESIS (FIG. 3.2.1)

- Eicosanoids are synthesized locally in most tissues from arachidonic acid (Arachidonic acid metabolism).
- The cyclo-oxygenase (COX) pathway generates PGs and TXs while
- Lipoxygenase (LOX) pathway generates LTs.
- There are 2 cyclo-oxygenase isozymes viz. COX-1 and COX-2.
- Eicosanoids from COX-1 are present in almost all cells, and mainly take part in physiological functions, while those produced by COX-2 result in inflammatory and pathological changes.
- All products of COX pathway are metabolized by oxidation and excreted in urine.

Prostaglandins and Thromboxanes

- In 1930s, it was found that human semen contains a substance that contracts uterine smooth muscle.

- As this substance was thought to originate in the prostate, they called it 'Prostaglandin'. But it was later found to be produced in many tissues.

Actions

The eicosanoids act through their specific receptors present on the tissues.

CVS

- Prostacycline causes vasodilation while
- TXA_2 causes vasoconstriction.
- PGE_2 and $\text{PGF}_2\alpha$ are weak cardiac stimulants.

GIT

- PGs and TXs stimulate gastrointestinal smooth muscle in colic and watery diarrhea.
- PGE_2 inhibits gastric secretions and enhances mucous production. Thus they have a protective effect on gastric mucosa.

Airways

- PGE_2 and PGI_2 relax bronchial smooth muscles with TXA_2 and $\text{PGF}_2\alpha$ contract them.
- They may have a protective effect on gastric mucosa.

Platelets: TXA_2 induces platelet aggregation while PGI_2 inhibits platelet aggregation.

Uterus

- PGE_2 and $\text{PGF}_2\alpha$ contract human uterus which is more sensitive to PGs during pregnancy.
- They also soften the cervix. Thus PGs may be involved in the initiation and progression of labor. PGs are produced by fetus during labor.
- PGs present in the semen may facilitate movement of sperms and fertilization by coordinating the movement of the uterus.
- They also play a role in dysmenorrhea and menorrhagia.

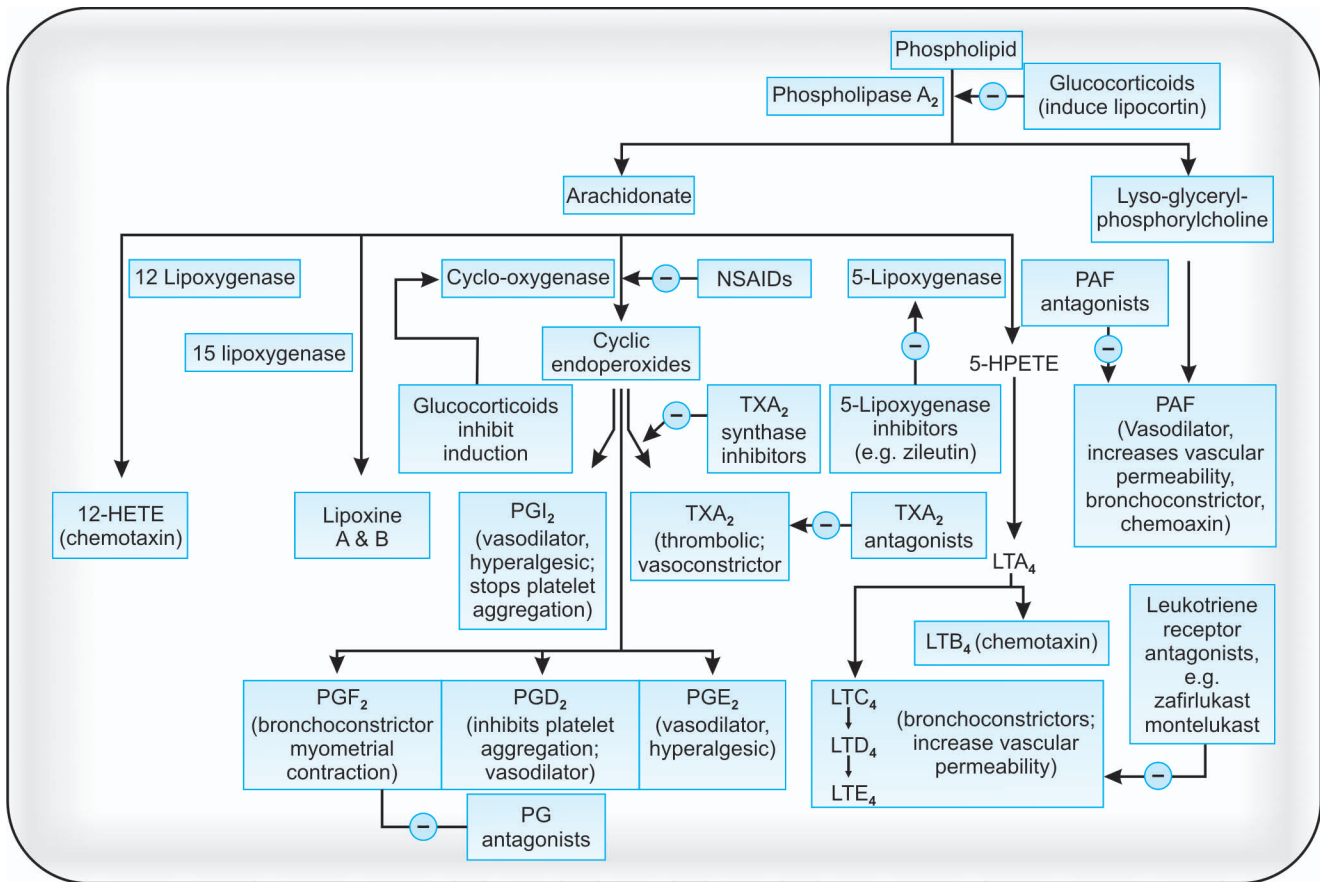


Fig 3.2.1: Metabolism of arachidonate via cyclo-oxygenase and lipo-oxygenase pathway with synthesis of eicosanoids and prostanoids

Kidneys: PGE₂ and PGI₂ cause renal vasodilatation and have a diuretic effect.

CNS: PGs increase body temperature when administered into cerebral ventricles. They also induce sleep.

Nerves

- PGs sensitize sensory nerve endings to pain and on intradermal injection cause pain.
- They have a role in the genesis of inflammation.

Bone: PGs stimulate bone reabsorption and formation.

Adverse effects: Depend on the type of PGs, dose and route. Diarrhea, nausea, vomiting, fever, hypotension and pain due to uterine contractions are common.

Uses

- Gynecological and obstetrical:
 - Abortion:** For I and II trimester termination of pregnancy and ripening of cervix during abortion, PGE₂ and PGF₂α are used. They are also used with

mifepristone to ensure complete expulsion of the products of conception.

- Facilitation of labor:** As alternative to oxytocin in patients with renal failure.
 - Cervical priming:** Intravaginal PGE₂ is used.
 - Postpartum hemorrhage:** Intramuscular PGF₂α is used as an alternative to ergometrine.
- Gastrointestinal: **Peptic ulcer** : PGE₁ (misoprostol) and PGE₂ (enprostil) are used for the prevention of peptic ulcer in patients on high dose NSAIDs.
 - Cardiovascular:
 - Patent ductus arteriosus:** Patency of fetal ductus arteriosus depends on local PGs synthesis. In neonates with some congenital heart disease, patency of the ductus arteriosus is maintained with PGs until surgery is done.
 - To prevent platelet aggregation during hemodialysis.
 - Other uses:** PGs are used in pulmonary hypertension and some peripheral vascular diseases. They can also be used in open angle glaucoma to lower intraocular pressure.

LEUKOTRIENES

'Leuko' – because they are found in white cells (leucocytes); 'trienes' – they contain triene system of double bonds.

- Leukotrienes (LT) are products of arachidonic acid metabolism synthesized by the lipoxygenase pathway and are found in the lungs, platelets, mast cells and white blood cells.
- LTA_4 is the precursor from which LTB_4 , LTC_4 , LTD_4 , LTE_4 and LTF_4 are derived.
- LTC_4 , LTD_4 and LTE_4 are together known as slow reacting substances (SRS-A) of anaphylaxis.
- The LTs produce their effects through specific receptors.

Actions

- Leukotrienes cause vasoconstriction, increase vascular permeability leading to edema, increase airway mucous and are potent bronchiolar spasmogens.
- Given subcutaneously they cause wheal and flare.
- Leukotrienes have a role in inflammation including rheumatoid arthritis, psoriasis and ulcerative colitis. They also contribute to bronchial hyper-responsiveness in bronchial asthma.

Drugs that inhibit lipoxygenase and thus block the synthesis of leukotrienes are under investigation in the treatment of bronchial asthma.

PLATELET ACTIVATING FACTOR (PAF)

- PAF is an important mediator in acute and chronic, allergic and inflammatory phenomena.
- PAF is a lipid released from inflammatory cells on stimulation and acts on specific receptors.
- It causes local vasodilation resulting edema, hyperalgesia and wheal formation.

- It is potent chemotaxin for leukocytes and a spasmogen on bronchial and intestinal smooth muscles. It is a mediator of inflammation.

Cytokines: They are peptide product derived mainly from:

1. Macrophages
 2. Lymphocytes
 3. Leukocytes, endothelial cells and
 4. Fibroblast.
- They act as regulator of inflammation and immune reactions.
 - Some are involved in multiplication and differentiation of cells.
 - **Examples of cytokines are** Interleukins (1 to 10), Interferons, Tumor Necrotic Factor (TNF), Platelet derived growth factor (PDGF), Transforming growth factor ($TGF-\beta$), Chemokines, Colony stimulating factors (CSF).
 - They act in a complex interconnecting network Leukocytes, vascular endothelial cells, mast cells, fibroblasts, hemopoietic stem cells and osteoclasts controlling proliferation activation through autocrine or paracrine mechanism.
 - **IL-1** is an important inflammatory mediator, involved in several important chronic inflammatory conditions and autoimmune diseases such as Rheumatoid arthritis.
 - **Interferon alfa, beta and gamma** have antiviral activity and interferon gamma has significant immunoregulatory functions.

Clinical use of Interferon: They are used in various cancer therapy and in viral infections. Interferon beta is used in the treatment of multiple sclerosis, while interferon gamma is used in the treatment of hepatitis (under trial), leishmaniasis and leprosy.

5-HT (Hydroxytryptamine) Ergot Alkaloids, Angiotensins and Kinins

SEROTONIN

Vasoconstrictor substance which appeared in serum, when blood clotted.

ENTERAMINE

Smooth muscle contracting substance present in enterochromaffin cells of gut mucosa.

- Later on it was discovered that both are same.

Introduction

- 5-Hydroxytryptamine (serotonin) was isolated in 1948.
- It is found in various plant and animal tissues.
- A large volume of information on 5-HT is now available and has been of great pharmacological interest.

Distribution, Synthesis and Degradation

- In human body, 5-HT is present in the intestines, platelets and brain.
- It is synthesized from the amino acid tryptophan and stored in granules.
- It is degraded mainly by MAO and Dehydrogenases (Fig. 3.3.1).

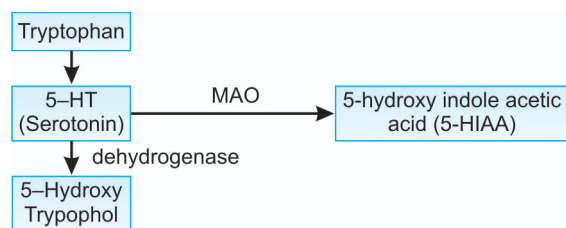


Fig. 3.3.1: Degradation of tryptophan

5-HT Receptors

- The actions of serotonin are mediated through its receptors.
- Seven types of 5-HT receptors (5-HT₁₋₇) with further subtypes of 5-HT₁ and 5-HT₂ receptors are presently known.
- 5-HT₁ receptors are further subdivided into 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D}.
- 5-HT₂ receptors are further subdivided into 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}.
- For many receptor—selective agonists and antagonists are being developed.

Pharmacological Actions

CVS

- The action on blood vessels is complex. Biphasic response is produced.
- Large vessels (arteries, veins and venules) are constricted and is due to direct action of serotonin on 5-HT_{2A} receptor.
- While arterioles dilate. It is due to action of serotonin on 5-HT₁ receptor as well as partly due to releasing of NO.
- A characteristic triphasic response is seen on blood pressure following IV injection.
 - Initial fall in BP is due to increased vagal activity
 - Rise in BP—due to vasoconstriction of large vessels, followed by
 - Fall in BP—due to arteriolar dilation.

GI tract

(5-HT) Increases GI motility and increases contraction resulting in diarrhea.

It also inhibits gastric secretion of acid and pepsin

(5-HT) increases mucus production (ulcer healing property).

Platelet: 5-HT causes:

- Change in the shapes of platelets

- ii. Platelets aggregation
- iii. If endothelium intact: Vasodilatation, but if endothelium damaged: Vasoconstriction.

Nerve Endings: 5-HT stimulates nociceptive (pain mediating) sensory nerve endings.

CNS

- Poorly crosses BBB, and reduces CNS effects.
- 5-HT is a neurotransmitter in the CNS.

Physiological and Pathophysiological Role

- 5-HT is postulated to be having a role in peristalsis, vomiting, platelet aggregation, homeostasis and inflammation.
- It is also thought to initiate the vasoconstriction in migraine.
- It is also thought to have neurotransmitter, neuroendocrine functions.
- It has some role in Raynaud's phenomenon, variant angina, Hypertension, etc.

Drugs Action on 5-HT Receptors

- Serotonin has no therapeutic uses.
- However, its receptor agonists and antagonists have been used in various conditions.

Serotonin Agonists (Table 3.3.1)

Sumatriptan

- A 5-HT_{1D} agonist effective in the treatment of acute migraine and cluster headache.

- Given orally/SC at the onset of an attack, sumatriptan relieves headache and also suppresses nausea and vomiting of migraine. It is short-acting.

Adverse effects include dizziness, altered sensations, weakness, chest discomfort and neck pain. It is contraindicated in coronary artery disease.

Other Agonists

Buspirone is a 5-HT_{1A} agonist-antagonist used as an anti-anxiety agent.

Dexfenfluramine is used as an appetite suppressant.

α-methyl HT. agonist of 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}.

Metachlopromide and Cisapride: 5HT₄ agonist

Serotonin Antagonists

Cyproheptadine

- It blocks 5-HT₂, H₁ histamine and cholinergic receptors.
- It increases appetite and is used to promote weight gain especially in children.
- It is also used in carcinoid tumors.

Methysergide: 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} inhibitor

Ketanserin

- Blocks 5-HT₂ receptors and antagonises vasoconstriction and platelet aggregation promoted by 5-HT.
- It is used in hypertension.

Table 3.3.1: Serotonin agonists, antagonists and their therapeutic uses

	Receptor	Uses	Comments
AGONISTS			
Sumatriptan	5-HT _{1D}	Acute migraine Cluster headache	Short-acting; may need repetition of dose
Buspirone	5-HT _{1A} (Agonist-antagonist)	Anxiolytic Appetite suppressant	Patients should be carefully monitored for risk of pulmonary hypertension
ANTAGONISTS			
Cyproheptadine	5-HT ₂ ; H ₁ histamine and muscarinic receptors	Appetite stimulant Carcinoid tumors	—
Ketanserin	5-HT ₁ and 5-HT ₂	Hypertension	Also antagonizes platelet aggregation promoted by 5-HT
Ondansetron	5-HT ₃	Antiemetic	—

Ondansetron

- It is a 5-HT₃ antagonist used in the prevention and treatment of vomiting due to surgery and cancer chemotherapy.
- Many other drugs including some antihistamines also block serotonin receptors.

Atypical Neuroleptics: Clozapine and Risperidone also block's 5HT receptors.

ERGOT ALKALOIDS (Table 3.3.2)

- Ergot alkaloids are produced by *claviceps purpurea*, a fungus that infects rye, millet and other grains.
- Consumption of such grains results in 'ergotism' manifested as gangrene of hands and feet, hallucinations and other CNS effects.
- Barger and Dale isolated ergot alkaloids in 1906.

Natural ergot alkaloids include ergometrine, ergotamine, ergotoxine. The semisynthetic dehydrogenated derivatives are also available.

Actions

- Ergot alkaloids have agonistic, partial agonistic and antagonistic actions at 5-HT and alpha adrenergic receptors and agonistic actions at CNS dopamine receptors. Thus their actions are complex.
- Some of them are powerful hallucinogens, e.g. lysergic acid diethylamide (LSD).
- They cause stimulation of smooth muscles—some mainly vascular smooth muscles and other mainly uterine smooth muscles.
- The vasoconstrictor effect is responsible for gangrene.

Adverse effects

- Nausea, vomiting and diarrhea are common.
- Prolonged use results in gangrene due to persistent vasospasm.
- Methysergide causes retroperitoneal and mediastinal fibrosis.

Uses

1. Migraine
2. Postpartum hemorrhage—ergometrine is used.

Drugs Used in the Treatment of Migraine

Migraine: Migraine is a common disorder characterized by severe, throbbing, unilateral, headache often associated with nausea, vomiting and fatigue lasting for several hours. In the classical migraine, a brief 'aura' of visual disturbances occurs prior to the headache.

Triggering factors

- An attack is triggered by factors like stress, anxiety, excitement, food (like chocolate and cheese) and hormonal changes.
- These triggering factors stimulate the release of vasoactive substances from nerve endings which are responsible for the events of headache.
- However the exact pathophysiology is not understood and several hypotheses have been put forward.

Drugs Used in Acute Attacks

- Aspirin, paracetamol or other NSAIDs are effective.
- Drug should be taken at the initiation of attack.
- Metoclopramide can be combined with aspirin as it is an antiemetic and also speeds up absorption of aspirin.
 - **Ergotamine** should given orally (or via sublingual/rectal routes when vomiting is present)
 - **Sumatriptan** is very effective but short-acting.

Prophylaxis: When the attacks are frequent and severe, prophylaxis is needed. Drugs used for the prophylaxis are:

- β -adrenergic blockers: Propranolol reduces frequency and severity of attacks.
- Ca⁺⁺ channel blockers: Flunarizine may be useful.
- Pizotifen and cyproheptadine block 5-HT and H₁ histamine receptors; may be used as an alternative.
- Tricyclic antidepressants: Amitriptyline may be tried.
- Methysergide blocks 5-HT receptors but due to adverse effects like retroperitoneal fibrosis, it is not preferred.

ANGIOTENSINS

Angiotensins are peptides synthesized from the precursor angiotensinogen.

- Angiotensinogen, a circulating protein synthesized in the liver and is converted sequentially to angiotensin I, angiotensin II and angiotensin III.

Table 3.3.2: Ergot alkaloids

Ergotamine	5-HT ₁ Partial agonist/antagonist	Acute attack of migraine	—
Ergometrine	5-HT ₁ Partial agonist/antagonist	Postpartum hemorrhage	—
Methysergide	5-HT ₂ Antagonist/partial agonist	Prophylaxis of migraine	Not preferred due to risk of retroperitoneal and mediastinal fibrosis

- Angiotensin converting enzyme is widely distributed in the body. It is present in blood vessels, kidneys, heart, brain, lungs, adrenals and other tissues.
- Angiotensin II, the most potent angiotensin agonist acts through angiotensin receptors (AT_1 and AT_2) present on the tissues.

Synthesis and metabolism of angiotensins is described in figure 3.3.2.

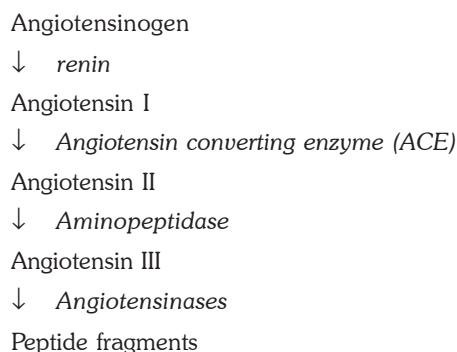


Fig. 3.3.2: Synthesis and metabolism of angiotensins

Actions

- It stimulates the synthesis of aldosterone by the adrenal cortex, increases sodium reabsorption by the kidneys and increases secretion of vasopressin.
- Angiotensin II causes vasoconstriction resulting in increased blood pressure.
- Angiotensin II also promotes the growth of vascular and cardiac muscle cells and may play a role in the development of cardiac hypertrophy as in hypertension.
- By these actions, renin-angiotensin system regulates the fluid and electrolyte balance and blood pressure.

Inhibitors of ACE and blockers of angiotensin II receptors are now used in the treatment of hypertension, congestive heart failure and other conditions that are due to excess of angiotensin II activity

KININS

- Kinins are a group of vasodilator peptides formed and is responsible for pain sensation.
 - Kallidin (decapeptide)
 - Bradykinin (nonapeptide).

They are synthesized from the precursor HMW kininogen by the action of the enzymes called kallikreins.

Kallikreins

- Kallikreins are present in the plasma, kidneys, pancreas, intestines, salivary glands and other tissues.
- They are serine proteases like trypsin.
- They are glycoprotein.
- Tissue kallikreins: Kallidins
- Plasma kallikreins (circulate in blood): Bradykinin.

Kininogen

- Precursor of kinin
- It is present in plasma, lymph, interstitial fluid
 - Low molecular weight form: (LMW kininogen)
 - High molecular weight form (HMW kininogen)
- Both are acidic glycoproteins
- HMWK: Confined to blood stream
- LMWK: Crosses capillary wall and serve as substrate for kallikrein.

Kinins are rapidly degraded by kinase II which is same as ACE and has a very short $t_{1/2}$ (< 15 seconds).

Actions

- Kinins produce their actions by acting through B_1 and B_2 receptors.
- Kinins are potent vasodilators and cause a brief fall in BP.
- Intradermal injection produces **Red spot, wheal and flare** just like histamine (triple response)
- They stimulate contraction of other smooth muscles—thus they induce bronchospasm in asthmatics, slow contraction of intestines (Brady—slow) and uterus.
- Kinins mediate inflammation, and stimulate the pain nerve endings.
- Kinins also modulate the tone of salivary and pancreatic duct. They also regulate transport of water, ions, glucose, etc across the epithelial cells of GIT and Kidney.

Drugs affecting the kallikrein-kinin system— B_1 and B_2 antagonists are now being developed.

Pathophysiological role:

- Mediation of inflammation
- Mediation of pain
- Functional Hyperemia
- Production of clotting component.
- Closure of ductus arteriosus
- Involve in shock, rhinitis, pancreatitis and immunological reactions.



S E C T I O N

4

Respiratory System

Cough and Its Management

COUGH AND DRUGS USED IN THE TREATMENT OF COUGH

Cough: Cough is one of the most common symptom of respiratory diseases. It is a protective reflex—to expel out unwanted material, excessive secretions or foreign particles from the respiratory tract. It could be due to infection, allergy, pleural diseases and malignancy. Cough is of two types: Productive and Non-productive.

Productive Cough: Here coughing results in removal of secretions or foreign particles. It is also called useful (serves the purpose) cough. It is commonly seen in Bronchial Asthma, acute and chronic Bronchitis, Bronchiectasis, Pneumonia, Pulmonary Tuberculosis (expectorants to be avoided), Lung cancer, etc.

- This type of cough is symptomatically treated with drugs like the expectorants, mucolytics or with steam inhalation. Antimicrobial agents may or may not be used (depending on the presence or absence of bacterial infection).

Note

- This type of cough should not be suppressed (unless stress of coughing must be avoided).
- Drugs that tend to increase the viscosity of the secretions by drying it such as anti-cholinergics and anti-histaminics (due to their anti-cholinergic property) should be avoided in productive cough.

Non-productive or Dry-irritating Cough: It results from irritation in the respiratory tract because of the dust or fumes or other environmental pollutants. It is also seen in **Upper Respiratory Tract Infections** (e.g. Pharyngitis). Coughing does not result in removal of anything (very little or no sputum) from the respiratory tract, does not serve any purpose and therefore it is also called ‘useless’ cough.

- Dry cough is treated with **cough suppressants** mainly acting centrally, or ‘peripherally acting suppressants’ or

anti-histaminics or rarely with expectorants (only for irritation below the epiglottis).

Note: That the treatment of the two types of cough are different.

Classification

1. Pharyngeal demulcents: Lozenges, Cough drops, Linctuses.
2. Expectorants: Potassium iodide, Guaiphenesin, Ammonium, chloride, Ipecacuanha.
3. Central cough suppressants: Codeine, Noscapine, Dextromethorphan, Antihistamines, Benzonatate.

Drugs Used in the Treatment of Productive Cough

Expectorants: Expectorants (Latin—expectorate=to drive from the chest). They are the drugs that help in removal (expectorating out) of sputum. Expectorants increase water content of the respiratory secretions making them more thin and easy to remove. Total volume of secretions (sputum) increase.

Examples: Potassium iodide, Potassium citrate, Sodium citrate, Ammonium chloride, Ipecacuanha, Vasaka, Terpin hydrate, Eucalyptus oil, Guaiphenesin, Guaiacol, etc.

- Direct stimulants Volatile oils like eucalyptus oil; creosotes, alcohol, cedar wood oil—when administered by inhalation with steam can increase respiratory secretions.
- Reflex expectorants are given orally, they are gastric irritants and reflexly increase respiratory secretions.
- Potassium iodide, acts both; directly and reflexly. Ipecacuanha is an emetic. In subemetic dose it is used as an expectorant.

Extemporaneous Expectorant Formulation: (One dose)

- i. Potassium iodide 0.2 g
- ii. Potassium citrate 1.0 g

- iii. Sodium bicarbonate 1.0 g
- iv. Tincture ipecacuanha 0.6 ml
- v. Syrup tolu 2.0 ml
- vi. Water up to 30.0 ml.

Mucolytics: Mucolytics liquify the sputum by breaking down muco-polysaccharide strands. Liquifaction helps in easy removal of the secretions. They do not increase the water content or total volume of the secretions.

Examples: Bromhexine, Ambroxol, Serratiopeptidase, Carbocysteine, Acetylcysteine

- Normally the respiratory mucous is watery. The glycoproteins in the mucous are linked by disulphide bonds to form polymers making it slimy link the glycoproteins in the mucous.
- In respiratory diseases, the glycoproteins form larger polymers with plasma proteins present in the exudate and the secretions become thick and viscid. Mucolytics liquify the sputum making it less viscid so that it can be easily expectorated.
- *Bromhexine* obtained from the plant *Adhatada vasica* is a good mucolytic. It depolymerises the mucopolysaccharides in the mucous. It is given orally (8-16 mg thrice daily). Side effects are minor-may cause rhinorrhea.
- Acetylcysteine opens disulfide bonds in mucoprotein of the sputum reducing its viscosity. It is given by aerosol. Side effects are common and hence not preferred.
- Carbocysteine is similar to acetylcysteine and is used orally.

Steam inhalation offers an effective and inexpensive alternative to drugs. In presence of dehydration, just rehydrating the patient is found to be beneficial.

Note: Expectorants and Mucolytics, both have similar indications (uses) - in treatment of 'Productive' cough - where there are excessive, thick and tenacious secretions which are difficult to remove. As they act by different mechanisms, they may be used together.

Decongestants: Decongestants are the drugs that reduce mucosal congestion resulting from allergic or inflammatory reaction. These are sympathomimetic agents. They relieve congestion by vasoconstrictor action (with possible cardiovascular side effects - caution in elderly). They are also used as nasal decongestants.

Examples: Phenylephrine, Phenylpropanolamine, Pseudoephedrine, Ephedrine, Oxymetazoline

Pharyngeal Demulcents: Pharyngeal demulcents (demulcere=to care soothingly-in LATIN). These drugs increase the flow of saliva which produces a soothing effect

on the pharyngeal mucosa and reduce afferent impulses arising from the irritated mucosa.

- Dry cough due to irritation of the pharyngeal mucosa is relieved. Candy sugar or a few drops of lemon also serve this purpose.

Bronchodilators: These are the agents, which relieve cough that is resulting from bronchospasm.

- The antitussive preparations generally have a combination of a central cough suppressant, an expectorant, an antihistaminic and sometimes a bronchodilator and a mucolytic agent.

Drugs Used in Treatment of Non-productive Cough

Centrally Acting Cough Suppressants: They inhibit the medullary cough center and thereby inhibit the 'reflex'. They should be used ONLY in non-productive cough (i.e. without sputum), to suppress the cough reflex arising out of irritation.

Examples: Codeine, Pholcodeine, Noscapine, Dextromethorphan, Ethylmorphine.

Note

- Cough suppressants SHOULD NOT BE USED in cases with productive cough.
- Cough suppressants should not be COMBINED with expectorants or mucolytics - it amounts to combining two drugs with opposite actions.
- Central cough suppressants act by inhibiting cough centre in the medulla (CNS).
- Codeine is a good antitussive with less addiction liability; nausea, constipation and drowsiness are common. Does 10-15 mg every 6 hours.
- Noscapine is a potent antitussive; no other CNS effects are prominent in therapeutic doses. Nausea is the only occasional side effect. Dose 15-30 mg every 6 hours.
- Dextromethorphan and pholcodeine are synthetic opioid derivatives with antitussive actions like codeine but with less side effects. Pholcodeine is longer-acting-given twice daily.
- Benzonatate is chemically related to the local anesthetic procaine. It acts on the cough receptors in the lungs and also has a central effect. It is given orally-100 mg thrice daily.
- Antihistamines are useful in cough due to allergy except that due to bronchial asthma.

Antihistaminics: Histamine is one of the mediators of allergic reaction. Anti-histamines antagonize (block) the actions of histamine. This may be useful in patients with cough due allergic conditions. Some of them have CNS depressant

properties and cause sedation. Such antihistaminic also depress cough center. Extra caution is required while using such drugs that cause sedation during day time as they slow down body reflexes and this may be dangerous during driving a vehicle and handling machines. Some antihistaminics have anticholinergic activity also. They tend to make secretions more thick and tenacious. This is not desirable if the patient has productive cough.

Examples: Triprolidine, Terfenadine, Azatidine, Diphenylpyraline (less sedation, less anti-M), Chlorpheniramine maleate, Pheniramine maleate (sedatives), Promethazine, Diphenhydramine, Carbinoxamine, Methdilazine (pronounced sedation + Anti-Muscarinic).

Soothing agents: Popular among the cough remedies is the cough-drops available in the form of lozenges. Their action is simply to increase salivation (sialagogues) which lubricates upper pharynx and thereby reduces irritation. Such drugs are however not effective if the irritation is deep seated (below epiglottis). So called 'medicated' lozenges containing menthol, eucalyptus oil, etc. have value comparable only to placebo. A few lemon drops or a lump of sugar serves similar purpose.

Trade Preparations: Formulations available in the market (and listed as cough remedies) contain 57 different drugs in different combinations which can be placed under 8 different categories :

- Expectorants
- Mucolytics
- Central cough suppressants
- Anti-histaminics
- Bronchodilators
- Decongestants
- Correctives and preservatives
- Miscellaneous

- As against this, WHO Essential Drug List for treatment of cough includes only one drug (Codeine). As per the National Formulary 4-5 ingredients are sufficient for an Expectorant and only 1-2 as cough suppressant.
- Availability of large number of products in the market, requires that a doctor should be able to select the right formulation and avoid undesirable drug combinations, in different clinical settings.

Bronchodilators: They cause relaxation of bronchial smooth muscles. This is believed to relieve cough resulting from spasm of the smooth muscles. Stimulation of β_2 receptors inhibit the release of Histamine and other mediators from mast cells, this may be an additional mechanism for the use of such drugs in treatment of cough associated with allergic conditions.

Examples: Terbutaline (β_2), Salbutamol (β_2), Ephedrine ($\alpha+\beta$), etc.

Doses of some commonly used ingredients in cough remedies:

Expectorants: These are included in expectorant formulations in different combinations, given 3-4 times a day.

Potassium Iodide	: 200-300 mg
Potassium Citrate	: 1-2 g
Sodium Citrate	: 1-2 g
Ammonium chloride	: 300 mg
Ipecacuanha syrup	: 0.6-1.0 ml
Vasaka	: 1-2 ml
Eucalyptus oil	: 0.06-0.2 ml
Guaiaacolate	: 100-200 mg
Terpin hydrate	: 200 mg 4 hourly

Guaiphenesin : 400 mg in adults;
in children: 2-6 yrs = 50-100 mg;
6-12 yrs = 100-200 mg (given 4 hourly)

Bronchial Asthma and Its Management

Bronchial Asthma: Bronchial Asthma (asthma = difficulty in breathing) results from spasm of bronchial smooth muscles, narrowing of bronchial lumen and increased airway resistance. (differs from Cardiac Asthma). Spasm of bronchial smooth muscles may be due to the release of chemical mediators of allergy or due to irritation. Inflammatory process in the bronchial mucosa adds to, and in many cases of acute attack of asthma, is the cause of increased airway resistance. Thus asthma can be viewed as a disease with allergic - cum - inflammatory basis (Figs 4.2.1 and 4.2.2).

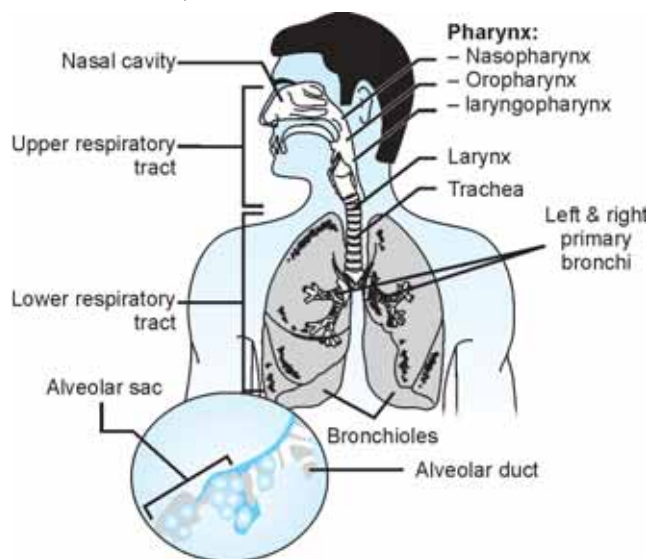


Fig. 4.2.1: Anatomy of respiratory system

- The tracheobronchial smooth muscle is hyperresponsive to various stimuli like dust, allergens, cold air, infection and drugs. These trigger factors trigger an acute attack. Antigen-antibody interaction on the surface of mast cells cause:
 - i. Degranulation of mast cells releasing stored mediators of inflammation.
 - ii. Synthesis of other inflammatory mediators which are responsible for bronchospasm, mucosal congestion and edema. Inflammation is the primary pathology.

- ii. Synthesis of other inflammatory mediators which are responsible for bronchospasm, mucosal congestion and edema. Inflammation is the primary pathology.

Clinically 2 types of asthma are identified:

Extrinsic asthma: Starts at an early age, occurs in episodes; the patient has a family history of allergies less prone to status asthmaticus.

Intrinsic asthma: Starts in the middle age and assumes chronic form. There is no family history of allergies. More prone to status asthmaticus.

Classification

1. Bronchodilators
 - A. *Sympathomimetics*: Salbutamol, Terbutaline, Salmeterol, Adrenaline, Ephedrine.
 - B. *Methylxanthines*: Theophylline, Aminophylline.
 - C. *Anticholinergics*: Ipratropium bromide, Atropine.
2. Anti-inflammatory agents
 - A. *Systemic*: Glucocorticoids, Hydrocortisone, Prednisolone
 - B. *Inhalational*: Beclomethasone, Budesonide, Flunisolide, Triamcinolone
3. Mast cell stabilizers
Disodium cromoglycate, Nedocromil, Ketotifen.
4. *Newer drugs*

Sympathomimetic drugs (See ANS)

- These drugs are potent bronchodilators.
- They stimulate β_2 (beta) receptors in bronchial smooth muscles resulting in increased cAMP levels. This increased cAMP leads to bronchodilatation. The increased cAMP on mast cells inhibit the release of inflammatory mediators.
- They also reduce bronchial secretions and congestion (by action on α (alfa) receptors).

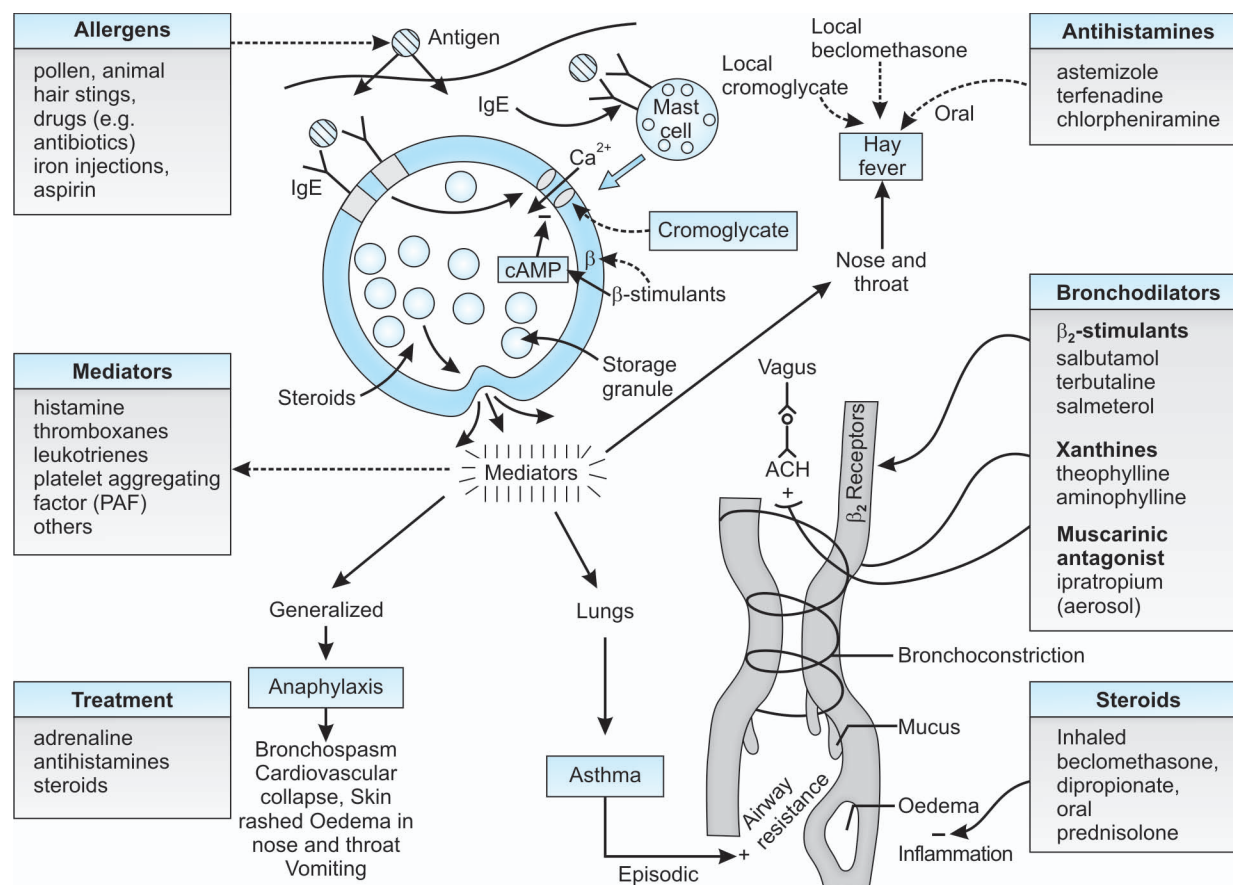


Fig. 4.2.2: Sketch diagram showing physiopathology of asthma, various factors and mediators of asthma and various drugs (classification) affecting it

Salbutamol (albuterol) and terbutaline

- They are selective β_2 agonists. Given by inhalation, they are fastest-acting bronchodilators with peak effect in 10 minutes.
- The action lasts for 6 hours. Adverse effects to β_2 agonists include muscle tremors, palpitation and nervousness.
- Selective β_2 agonists are the most commonly used bronchodilators as they are the most effective, fast-acting, convenient and relatively safe.
- They are available as **metered dose inhalers (MDI)**, **nebulizers** and also tablets for oral use. The proper technique in using the inhaler should be taught, 'Spacers' can be used in children and adults who cannot follow the right techniques for inhalation.
- Oral β_2 agonists have higher adverse effects and are used only in small children who cannot use inhalers and have occasional wheezing (1-4 mg 6 hourly).

Salmeterol/Formoterol

- It is a long-acting selective β_2 agonist. The onset of action is slow (hence not useful in acute attacks) but the effect remains for 12 hours.
- It is therefore used for longterm maintenance and for prevention of nocturnal asthmatic attacks.

Adrenaline, ephedrine and isoprenaline

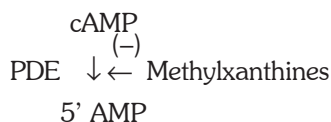
- Though adrenaline and isoprenaline produce prompt bronchodilation, they are not preferred due to the risk of adverse effects.
- Ephedrine produces bronchodilation but is slow in onset. Because of low efficacy, side effects and availability of better drugs, ephedrine is not preferred.

METHYL-XANTHINES

Theophylline and its derivatives like **aminophylline** are good bronchodilators. Caffeine is also imp. bronchodilator.

Mechanism of action

- Phosphodiesterase (PDE) is the enzyme that degrades cyclic AMP. Methylxanthines inhibit PDE and thereby enhance cAMP levels which brings about bronchodilation. cAMP also inhibits the release of mediators of inflammation.

**Pharmacokinetics**

- Aminophylline is given intravenously and slowly in acute attack of asthma not responding to β_2 agonists.
- In an acute attack, drugs given by inhalation may sometimes fail to reach the bronchioles because of severe bronchospasm. Intravenous aminophylline may then be tried. 250 mg aminophylline should be injected slow IV over 15-20 minutes.
- Rapid IV injection may cause collapse and death due to hypotension and arrhythmias. Convulsions can also occur and should be carefully watched for.

Adverse effects

- Theophylline is a drug of low therapeutic index.
- Gastric irritation, vomiting, insomnia, tremors, diuresis, palpitation, and hypotension are quite common. Higher doses cause restlessness, delirium, convulsions and arrhythmias. Children may therefore develop behavioral abnormalities on prolonged use-therefore it should be avoided.

Theophylline is a second line drug in bronchial asthma.

- Chronic asthma:** Oral theophylline can be used to control mild to moderate asthma. Etophylline +80% theophylline (Deriphylline) injection (IM) are used to relieve acute attacks. When used over a long-term. Plasma levels should be monitored.
- Acute severe asthma (status asthmaticus):** Intravenous aminophylline is tried when, sympathomimetics fail to relieve bronchospasm-but are found to be less effective.

ANTICHOLINERGICS: It relaxes bronchial smooth muscles but response is slower than sympathomimetics. *Ipratropium bromide* is given by inhalation and its action are largely confined to the respiratory tract. It is more effective in chronic bronchitis. It is safe and well-tolerated.

Uses

- As an adjunct to β_2 agonists.
- As a bronchodilator in some cases of chronic bronchitis.

ANTI-INFLAMMATORY DRUGS

Glucocorticoids: Glucocorticoids help primarily by their anti-inflammatory action. They also have immunosuppressant action. However, they have delayed onset of action. Systemic administration of steroids (Hydrocortisone, Prednisolone, etc.) should be avoided as long as possible because of their numerous side effects. Although steroids are not bronchodilators, beclomethasone inhalation helps in relieving acute attack (in combination with bronchodilators).

Mechanism of action

- Steroids are not bronchodilators.
- They suppress the inflammatory response to antigen-antibody reaction and thereby reduce mucosal edema and hyperirritability (hypersensitivity).
- They restore response to β_2 agonists if tolerance has developed. Oral prednisolone is commonly used for short term (5-7 day) therapy.

Inhaled steroids

- The use of inhalational steroids largely minimizes the adverse effects of steroids. But they are not effective in acute attacks and are only of prophylactic value. They prevent episodes of acute asthma, bronchial hyperreactivity and effectively control symptoms. The effect develops after 1 week of treatment.
- Side effects of inhaled steroids include hoarseness of voice, sore throat and oropharyngeal candidiasis. Rinsing the mouth and throat with water after each use can reduce the incidence of candidiasis and sore throat. No HPA axis suppression is seen in the recommended doses. *Beclomethasone dipropionate*, *budesonide*, *flunisolide* and *triamcinolone* are used as inhalers.

Does Beclomethasone, BECLATEINHALER 50,100 and 200 mg per metered dose ® 1-2 Puffs 3-4 times day.

- Acute exacerbation:** A short course (5-7 days) of oral prednisolone is given in addition to β_2 agonists.
- Chronic asthma:** Beclomethasone/Budesonide inhalation for a long period as prophylaxis.
- Status asthmaticus :** IV hydrocortisone hemisuccinate followed by oral prednisolone should be given.

MAST CELL STABILIZERS

Cromolyn sodium (disodium cromoglycate) was synthesized in 1965.

These are 'mast cell stabilizers'. They prevent the release of mediators of allergic reaction (histamine, SRS-A etc.), from the sensitized mast cells. They are useful in patients of chronic bronchial asthma for preventive purpose. Cromolyn sodium (disodium chromoglycate) is administered by inhalation while Ketotifen is given orally (more suitable in children).

Mechanism of action

- Cromolyn inhibits the degranulation of mast cells and thereby inhibits the release of mediators of inflammation.
- It thus prevents bronchospasm and inflammation following exposure to allergen. It is therefore used for prophylaxis. It is not a bronchodilator-hence not useful in acute episodes.
- Cromolyn sodium is used as an inhaler; it takes 2-4 weeks of treatment for the therapeutic benefit. Severe cough and bronchospasm can occur if administered with earlier spinhaler capsule formulation (due to particulate nature of drug).

Uses

1. Prophylaxis of bronchial asthma-Cromolyn sodium is used over a long period-2 puffs-3-4 times daily reduces episodes of acute asthma. Young patients with extrinsic asthma are more likely to be benefited.
2. Allergic rhinitis- Prophylactic nasal spray is used.
3. Allergic conjunctivitis- Eye drops are used prophylactically.

Nedocromil: It is similar to cromolyn sodium in its actions and uses. It is given twice daily.

Ketotifen

- It is an antihistaminic with actions like cromolyn sodium. It inhibits airway inflammation but it is not a bronchodilator.
- It is given orally. Beneficial effects are seen after 6-12 weeks of use. It is used for the prophylaxis of bronchial asthma and other allergic disorders like allergic rhinitis and conjunctivitis. Drowsiness and dry mouth are common side effects.

LEUKOTRIENE PATHWAY INHIBITORS

- Leukotrienes are involved in
 - (a) Various inflammatory reactions and in
 - (b) Anaphylaxis
- Leukotrienes [LTC_4 and LTD_4] are produced from the action of 5 lipoxygenase on Arachidonic acid and are synthesized by various inflammatory cells (i.e. mast cells) in the airway.
 - $\text{LTB}_4 \rightarrow$ Potent neutrophil chemo-attractive and
 - LTC_4 and LTD_4 Exerts various effects like bronchoconstriction in asthma.
- Zileuton - It is a potent 5 Lipoxygenase Inhibitor.

- Zafirlukast (Adult)/Montelukast (Child) - It is an LTD_4 antagonists
- These drugs are used in prophylaxis and management of chronic asthma.

Treatment of Asthma

Mild asthma: Inhaled β_2 stimulants.

Moderate asthma: Regular prophylaxis with cromoglycate. If symptoms persist inhaled steroids for prophylaxis. Acute episodes are managed inhaled β_2 agonists.

Severe asthma

1. Regular inhaled steroids.
2. Inhaled β_2 agonists 3-4 times a day.
3. Oral steroids may be considered.
4. Additional inhaled ipratropium bromide or oral theophylline may be given.

A. Management of acute attack (including status asthmaticus). Bronchodilators, glucocorticoids (as anti-inflammatory drugs).

B. Management of chronic asthma: Long-term use of bronchodilators, steroids, drugs that inhibit the release of mediators, etc. (and prevention of subsequent attacks)

Desensitization, if the allergen can be detected (which is very difficult), can bring long-term relief to the patient.

Status asthmaticus or acute severe asthma: It is an acute exacerbation. It is a medical emergency; may be triggered by an acute respiratory infection, abrupt withdrawal of steroid, drugs, allergens or emotional stress.

Treatment

- Nebulization of β_2 agonist and ipratropium alternately-every 30 minutes. Additional salbutamol 0.4 mg IM/SC may be given. Severe tachycardia should be watched for.
- Hydrocortisone hemisuccinate IV 100 mg stat followed by 100 mg every 8 hours infusion followed by a course of oral prednisolone
- Oxygen inhalation
- Antibiotics
- IV fluids to correct dehydration
- Aminophylline 250 mg slow IV over 15-20 minutes may be given carefully-watch for adverse effects
- Artificial ventilation may be required in extreme cases.



S E C T I O N

5

Blood

Drugs Affecting Hematopoiesis

HEMATINICS

Definition: Hematinics are compounds required in the formation of blood and are employed in the treatment of anemias.

Iron, vitamin B₁₂ and folic acid are essential for normal erythropoiesis.

IRON

Iron is essential for hemoglobin production.

Physiology

- The big percentage of iron in body stores is found in hemoglobin.
 - The ferric state of iron (Fe^{3+}) in methemoglobin is less able to carry oxygen than the ferrous form (Fe^{2+}) in hemoglobin.
 - Molecular oxygen is bound reversibly by the iron in hemoglobin.
- Inorganic iron in the (Fe^{2+}) is most readily absorbed from the GIT.
 - Men require a nutritional input of about 0.5-1 mg of iron per day.
 - Menstruating women require up to 2 mg of iron per day.
 - Pregnant women (especially in the last two trimesters of pregnancy) require 5-6 mg of iron per day.
- About 1 mg of iron is lost per day in the feces, sweat, and desquamated skin.
 - Menstruating women can lose up to 30 mg of iron per menstrual period.
 - Pregnant women can lose up to 500 mg of iron per full-term pregnancy.

- About 1 g of iron is stored as ferritin and hemosiderin in the bone marrow, liver, and spleen. This stored iron is available for the synthesis of hemoglobin if blood is lost from the body.
- Internal exchange of iron is mediated by a plasma transport protein, transferrin. Transferrin receptors on cell membranes mediate endocytosis of the transferrin-iron complex.

Distribution of iron in the body

Hemoglobin	66%
Ferritin, hemosiderin	25%
Myoglobin (in muscles)	03%
Enzymes(cytochromes, etc.)	06%

Daily requirement of iron

Adult male	0.5-1 mg
Adult female	1-2 mg
Pregnancy and lactation	3-5 mg

Dietary sources of iron. Food that is rich in iron are:

liver, egg yolk, meat, fish, chicken, spinach, dry fruits, wheat and apple.

Absorption

- The average Indian diet provides about 10-20 mg of iron.
- 10% of this iron is absorbed from the upper gut in the ferrous form.
- Ferric iron (Fe^{3+}) must be converted to ferrous iron (Fe^{2+}) for absorption in the GIT.
- During deficiency, absorption is better. Hem iron is better absorbed than inorganic iron.
- Absorption involves active transport into mucosal cells, from where it can be transported into the plasma and/or stored intracellularly as ferritin; in iron deficiency, the former route predominates.

Factors that influence iron absorption**Factors which increases iron absorption**

Ascorbic acid, acidic pH, meat, amino acids

Factors which decreases iron absorption

Antacids, phosphates, tetracyclines, phytates, presence of food in the stomach.

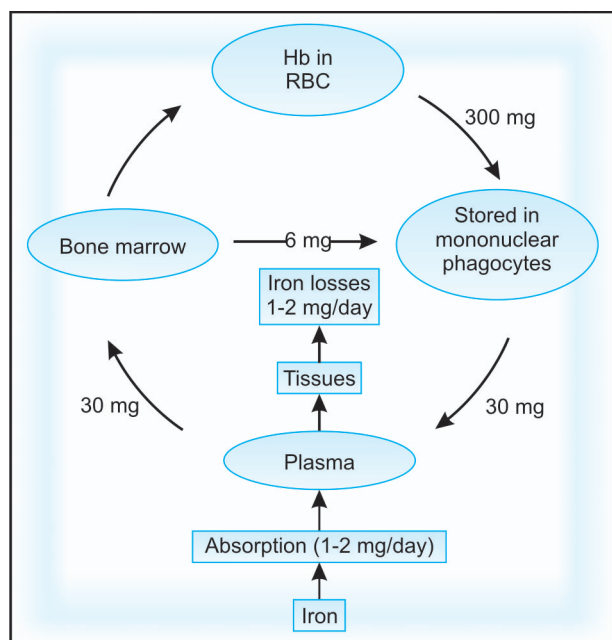


Fig. 5.1.1: Illustration showing distribution of iron in the body

Transport and distribution

- Iron in plasma is bound to and also transported with the help of a glycoprotein **transferrin** and stored as **ferritin** and **hemosiderin** in liver, spleen and bone marrow (Fig. 5.1.1).
- It is mostly used for erythropoiesis.
- Iron from, expired erythrocytes enters the plasma for re-use.

Excretion

- Daily 0.5-1 mg of iron is excreted.
- A large part is lost in shedding of intestinal mucosal cells and small amounts in the bile and desquamated skin. [Iron loss occurs mainly by (casting off) of ferritin-containing mucosal cells; iron is not excreted in the urine].
- In females, iron is also lost in menstruation.

Clinical use of iron

- Iron-deficiency anemia, which can be due to:
 - Chronic blood loss (e.g. with menorrhagia)
 - Increased demand (e.g. in pregnancy and early infancy)

- Inadequate dietary intake or absorption (uncommon in developed countries).

Pathophysiology of Iron Deficiency Anemia

Symptoms: Depletion of body iron can be associated with fatigability, anorexia, headache, and a characteristic hypochromic, microcytic anemia.

Laboratory findings

- A low plasma iron level in iron-deficiency anemia is associated with an elevated total iron-binding capacity of plasma transferrin, so that the ratio of serum iron to iron-binding capacity is less than 10%.
- Serum iron level: Total iron-binding capacity <10%. In other words, the serum iron carrier, transferrin, is less than 10% saturated with iron. This ratio in normal individuals is 35% + 15%.

Diagnosis: A definitive diagnosis of iron-deficiency anemia is made by confirming reduced bone marrow iron stores.

Complications: Severe iron deficiency can cause Plummer-Vinson syndrome, which is associated with dysphagia, hypopharyngeal webs, gastritis, and hypochlorhydria.

DRUGS FOR IRON DEFICIENCY ANEMIA

Preparations of iron: Iron is generally given orally—but can be given parenterally.

Oral iron preparations

Ferrous sulphate: 200 mg tab

Ferrous fumarate: 200 mg tab

Ferrous gluconate: 300 mg tab

Ferrous succinate: 100 mg

Iron calcium complex: 5% iron

Ferric ammonium citrate: 45 mg

Dose: Ferrous sulphate 3-4 tablets daily. The elemental iron content of different salts varies.

1. Ferrous sulfate, containing about 20% elemental iron, is the drug of choice for iron deficiency anemia.
2. Ferrous fumarate contains 33% elemental iron. It is principally used in multivitamin mineral mixtures.
3. Ferrous gluconate and ferrous choline citrate both contain 12% elemental iron.
 - Ferrous salts are better absorbed than ferric salts and are cheaper.
 - The last three preparations are claimed to be better tolerated but are more expensive.

- Expensive preparations of iron with vitamins, liver extract, amino acids, etc. are available but offer no obvious benefits.

Adverse effects of oral iron

- Epigastric pain, nausea, vomiting, gastritis, metallic taste, constipation (due to astringent effect) or diarrhea (irritant effect) are the usual adverse effects.
- Liquid preparations of iron cause staining of the teeth.

Parenteral Iron Preparations

Indications

1. When oral preparations are not tolerated
2. Failure of absorption – as in malabsorption, chronic bowel disease
3. Noncompliance
4. Severe deficiency with bleeding.

Preparations

- Iron dextran has 50 mg elemental iron/ml (2 ml ampoule) - can be given IM/IV. (maximum dose: 20 mg/kg/day)
- Iron—sorbitol-citric acid complex—contains 50 mg elemental iron/ml; given IM. Dose is to be calculated using a formula:

$$\text{Iron requirement (mg)} = 4.4 \times \text{body weight (kg)} \times \text{Hb deficit (g/dl)}$$

This also includes iron needed for replenishment of stores.

Parenteral Iron

- Intramuscular injection of iron is given deep IM in the gluteal region (buttocks) using 'Z' technique to avoid staining of the skin.
- Intravenous iron is given slowly over 5-10 minutes or as infusion after a test dose.
- Test dose = 25 mg.

Adverse Effects

- If given intramuscularly, iron dextran may cause local discomfort (pain at the site of injection), pigmentation (discoloration) of the skin, sterile abscess and potentially malignant skin changes.
- Headache, fever, arthralgias, difficulty in breathing and lymphadenopathy can occur.
- Anaphylactic reactions, although rare, can be fatal.

Acute iron poisoning

- It is common in infants and children in whom about 10 tablets can be lethal.
- Manifestations include vomiting, abdominal pain, hematemesis, bloody diarrhea, shock, drowsiness, convulsions, cyanosis, acidosis, dehydration, cardiovascular collapse and coma.

- Immediate diagnosis and treatment are important as death may occur in 6-12 hour.

Treatment

1. Supportive management and gastric lavage with sodium bicarbonate solution.
2. Desferrioxamine is the antidote. It is instilled into the stomach after lavage, to prevent iron absorption; dose: (15 µg/kg/hr.) should be injected IV/IM.
3. Correction of acidosis and shock.
4. Discuss the case with National Poisons Information Services [NPIS] or Drug Information Centers (DIC)

MEGALOBlastic ANEMIA

Megaloblastic anemia is characterized by the presence of **Macrocytic red cell precursors (megaloblasts)** in the blood and bone marrow.

Etiology of megaloblastic anemia

1. Megaloblastic anemia is almost always caused by deficiencies of vitamin B₁₂ or folic acid. These vitamins are essential in DNA synthesis, and thus, the high cell turnover in hematopoiesis is dramatically affected by deficiencies.
2. The most helpful diagnostic tests are evaluations of serum folate and vitamin B₁₂ levels, the Schilling test for urinary vitamin B₁₂ excretion, and analysis of gastric function.

DRUGS FOR MEGALOBlastic ANEMIAS

Folic acid and Vitamin B₁₂

- Folic acid and Vitamin B₁₂ are water soluble vitamins, belonging to the B-complex group.
- They are essential for normal DNA synthesis.
- Their deficiency leads to impaired DNA synthesis and abnormal maturation of RBCs and other rapidly dividing cells. This results in megaloblastic anemia.
- Vitamin B₁₂ and folic acid are therefore called maturation factors.
- Other manifestations of deficiency include *glossitis, stomatitis, malabsorption syndrome and neurological manifestations*.

Folic acid

1. Daily requirements

- a. Folic acid is found in a variety of foods, Its highest content found in *yeast, liver, and green vegetables*.
- b. The minimum daily adult dietary requirement is 50 µg, although pregnant or lactating women may need 100-200 (mcg) per day.

2. Physiology

- a. Folic acid is completely absorbed in the upper part of the small intestine.

- b. Folate present in food are in the reduced polyglutamate form. The mucosa of the duodenum and the upper jejunum contain *dihydro-folate reductase*, which methylates the reduces folate.
- c. Once absorbed, folate is transported to tissues where it is stored within cells as polyglutamate.
- d. Supplies are maintained by food intake and by the enterohepatic cycle.
- e. Folate and their cleavage products are mainly excreted through urine.
- f. Folic acid is a precursor of several coenzymes, and several derivatives of tetrahydrofolic acid are important in single carbon atom transfers, such as the synthesis of thymidylate from deoxyuridylate.

Prolonged cooking with spices destroys folic acid.

3. Deficiency

- a. Folate deficiency can result from (Fig. 5.1.2):
 1. Inadequate dietary supply.
 2. Disease involving the small intestine.
 3. Defects in the folate enterohepatic cycle (e.g., hepatic toxicity from alcoholism).
 4. Low concentration of folate-binding proteins in plasma
 5. Certain drugs (e.g., methotrexate, trimethoprim, anticoagulants, contraceptives)
 6. Normal pregnancy, which produces an increased requirement for folate
- b. Folate deficiency can result in megaloblastic anemia.
 1. The onset is more rapid than with a vitamin B₁₂ deficiency.

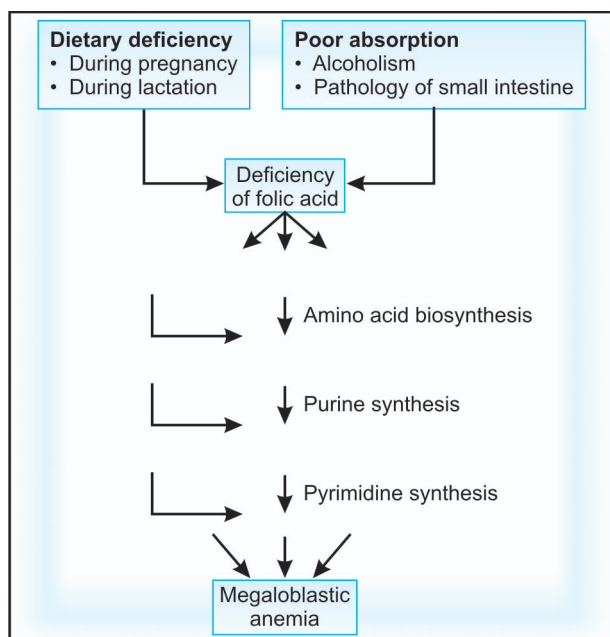


Fig. 5.1.2: Causes and effects of folic acid depletion

2. There is no neurological abnormality associated with folate deficiency.

4. Therapeutic uses

Folic acid is used:

- To treat megaloblastic anemia due to folate deficiency which can be caused by:
 - Poor diet (commonly in alcoholics)
 - Malabsorption syndrome
 - The use of some drugs, e.g. phenytoin
- Folic acid 2-5 mg/day is given orally along with vitamin B₁₂ in folic acid deficiency due to malabsorption syndromes. Folic acid is given IM to treat or prevent toxicity of methotrexate, (folate antagonist)
- Prophylactically in individuals at hazard from developing folate deficiency, for example:
 - Pregnant women (especially if there is a risk of birth defects).
 - Premature infants.
 - Prophylactically in pregnancy, lactation, infancy and other situations with increased requirement of folic acid = 500 mcg daily orally.
- Patients with severe chronic hemolytic anemia, including hemoglobinopathies (e.g. sickle cell anemia).

5. Preparations and administration

- a. Folic acid can be given orally (or parenterally) and usually cures an *uncomplicated megaloblastic anemia* resulting from folate deficiency.
- b. Folic acid injection contains sodium salt and is principally used in acute illness. It is given by intramuscular, intravenous, or deep subcutaneous injections.

6. Adverse effects

- a. The oral form of folic acid is nontoxic at therapeutic doses, but large amounts may counteract the antiepileptic action of phenobarbital, phenytoin, and primidone.
- b. There have been rare allergic reactions to parenteral administration.

Vitamin B₁₂: It is essential for cell growth and for maintenance of normal myelin. It is also important for the normal metabolic functions of folate (Fig. 5.1.3).

1. Physiology

- a. Vitamin B₁₂ (cyanocobalmin) is a cobalt-containing compound that is synthesized by the bacterial flora in the colon. However, it cannot be absorbed there, and humans must obtain the vitamin from the dietary intake of meat and vegetables that possess B₁₂.
- b. Intrinsic factor, a glycoprotein produced by the gastric parietal cells, is necessary for the gastrointestinal absorption of vitamin B₁₂.
 1. Gastric acid releases the vitamin from proteins, allowing it to form a complex with intrinsic factor.

2. The vitamin B₁₂-intrinsic factor complex binds to ileal mucosal cell receptors, from where it is transported into the circulation.
- c. Once in the circulation, vitamin B₁₂ is transported to the tissues by a plasma β -globulin- transcobalamin II.
- d. The liver preferentially stores vitamin B₁₂. A portion of the stored vitamin is secreted into the bile each day and is normally reabsorbed in the ileum.

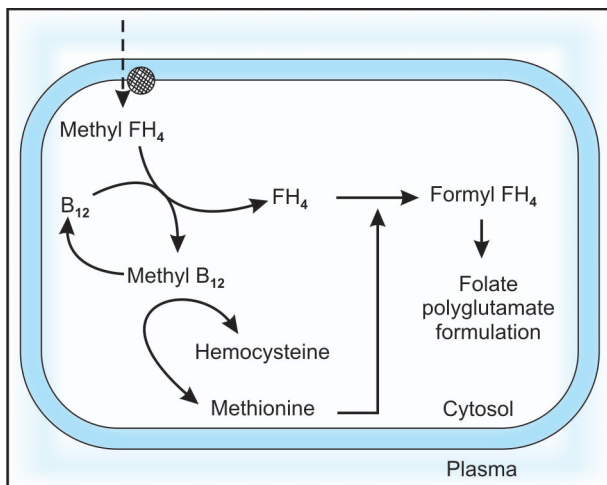


Fig. 5.1.3: The role of vitamin B₁₂ in the synthesis of folate polyglutamate

2. Deficiency

- a. Vitamin B₁₂ deficiency can result from:
 1. Inadequate secretion of intrinsic factor.
 2. Intestinal disorders, including ileac disease, gastric atrophy, or surgery.
 3. An insufficient dietary supply, although this is very rare.
 4. Congenital absence of transcobalamin II
 5. Interference with the reabsorption of vitamin B₁₂ excreted in the bile.
- b. Vitamin B₁₂ deficiency can result in:
 1. Megaloblastic anemia; although this is most common, all blood cell lines can be affected, resulting in pancytopenia.
 2. Demyelination and cell death, which can produce irreversible damage to the central nervous system (CNS) leads to neurological and neuropsychiatric disorders.

3. Therapeutic uses

- a. The most common therapeutic use for vitamin B₁₂ is the treatment of pernicious anemia (addisonian

anemia). This condition is usually caused by atrophy of the gastric mucosa with achlorhydria and failure to secrete intrinsic factor.

- b. Lifetime maintenance therapy with vitamin B₁₂ is required.

4. Preparations and administration

- a. If the patient lacks intrinsic factor or has ileac disease, vitamin B₁₂ must be administered parenterally. Cyanocobalamin injection, a bright red solution, is administered by the intramuscular or deep subcutaneous route, but never intravenously.
- b. Oral combinations of vitamin B₁₂ with intrinsic factor usually produce unreliable absorption; therefore, this approach is not recommended.
- c. Dose : 1000 mcg cobalamine im/week for 4-6 weeks followed by 1000 mcg im/months.
- Oral cobalamine 1000 mcg/day is a safe, effective and inexpensive alternate.

5. Adverse effects from vitamin B₁₂ administration are rare.

ERYTHROPOIETIN

Physiology

1. Erythropoietin is a glycoprotein hormone produced by the kidneys and released in response to tissue hypoxemia. It is a primary regulator of **erythropoiesis**.
2. Erythropoietin stimulates the proliferation of immature erythroid progenitor cells. These cell give rise to marrow normoblasts, the immediate precursors of reticulocytes and mature red blood cells.
3. Erythropoietin has been produced by recombinant DNA technology as a 165-amino acid glycoprotein.
 - a. It contains the identical amino acid sequence of isolated natural erythropoietin.
 - b. Antibodies to erythropoietin have not been detected.

Pharmacokinetics

1. Erythropoietin is administered parenterally (intravenously or subcutaneously) because it is broken down in the gastrointestinal tract.
2. The half-life ranges from 5-13 hours when administered intravenously to patients in chronic renal failure. The pharmacokinetics of erythropoietin are not affected by dialysis.

Therapeutic uses

1. Erythropoietin is indicated for the treatment of anemia associated with **chronic renal failure, including patients on and off dialysis**.
2. Erythropoietin **elevates or maintains red blood cell levels**, decreasing the need for transfusions.

3. Erythropoietin is not intended for patients needing immediate correction of severe anemia.
4. Recent data suggest that erythropoietin may also be useful for treating anemia in patients with AIDS who are being treated with zidovudine, but only in patients with low endogenous erythropoietin levels.

Adverse effects

1. Hypertension may occur.
2. Seizures may occur, especially during the first 90 days of treatment.
3. High doses of heparin may be needed for adequate anticoagulation during hemodialysis.

COLONY-STIMULATING FACTORS (CSF)

Physiology

1. CSFs are naturally occurring cytokine glycoproteins that stimulate the proliferation, differentiation, and activity of neutrophils, monocytes, and macrophages.
 - a. Granulocyte CSF (G-CSF) affects neutrophils.
 - b. Granulocyte-macrophage CSF (GM-CSF) affects neutrophils, monocytes, and macrophages.
2. Recombinant forms of these glycoproteins have been formed by cloning the genes for the CSFs.
 - a. **Filgrastim** is the synthetic form of G-CSF.
 - b. **Sargramostim** is the synthetic form of GM-CSF.

Filgrastim and Sargramostim

1. Pharmacological effects

- a. When administered to patients with normal bone marrow function, an increase in the number of white blood cells occurs within 2-3 days.
- b. In patients with bone marrow suppression, a similar increase occurs within 7-14 days. When these agents are administered to AIDS patients following zidovudine therapy, the number of neutrophils increase but the incidence of opportunistic infections remains the same.

2. Therapeutic uses

- a. These agents are used for the short-term treatment of patients with primary bone marrow deficiency states or following cancer chemotherapy or bone marrow transplantation
- b. In patients with aplastic anemia, administration of filgrastim and sargramostim increases the number of neutrophils and decreases infectious complications.

3. Administration: Filgrastim and sargramostim may be administered subcutaneously or intravenously.

4. Adverse effects

- a. Filgrastim can cause bone pain, splenomegaly, and abnormalities in uric acid concentrations and lactate dehydrogenase.
- b. Sargramostim can cause fluid accumulation, including pleural and pericardial effusions.

Hyperlipidemia and Hypolipidemics (Antihyperlipidemic Agents)

GENERAL CONSIDERATIONS

Classification of Lipoproteins:

Lipoprotein	Diameter	
1. Chylomicrons	100 nm	<i>Triglyceride > Cholesterol-E</i>
2. Chylomicrons remnant	50 nm	<i>Triglyceride > Cholesterol-E</i>
3. VLDL (very low density lipoprotein)	60 nm	<i>Triglyceride > Cholesterol-E</i>
4. IDL (intermediate low density lipoprotein)	30 nm	<i>Cholesterol-E > Triglyceride</i>
5. LDL (low density lipoprotein)	20 nm	<i>Cholesterol-E</i>
6. HDL (high density lipoprotein)	10 nm	<i>Phospholipid</i>

Note: IDL and LDL are more atherogenic

Plasma lipid levels (mg/dl)

	Low risk	Borderline	High risk
Total cholesterol	< 200	200–240	> 240
LDL Borderline	< 130	130–160	> 160
HDL High	> 60	35–60	> 35
Triglycerides	< 200	200–400	> 400

Classes of lipoproteins and transport pathways

Exogenous Pathways

- Chylomicrons are formed from dietary triglycerides and cholesterol.
- In adipose tissue and muscles, the enzyme lipoprotein lipase removes the triglycerides, leaving chylomicron remnants containing intact cholesterol esters.
- When chylomicron remnants reach the liver, they are taken up by hepatocytes (liver cells) and then cleaved, releasing free cholesterol.
- The cholesterol can be:
 - Stored in liver cell as cholesterol esters
 - Released in bile as cholesterol or as bile acids

- Used to form membranes or endogenous lipoproteins

Endogenous Pathways

- Very low-density lipoprotein (VLDL) is formed in the liver from triglycerides and cholesterol, generally as a result of high caloric intake.
- VLDL is released into the plasma, where lipoprotein lipase cleaves the triglycerides from VLDL.
- The hydrolysis of VLDL produces intermediate-density lipoprotein (IDL). The metabolic fate of IDL is twofold:
 - 50% of IDL again re-enter into liver, through binding with specific receptors.
 - Some IDL particles remain in the circulation, where triglycerides are removed so that IDL is eventually metabolized to LDL.
- LDL is involved in the transport of endogenous cholesterol ester to the liver or to extrahepatic tissues. LDL constitutes 60-70% of plasma cholesterol levels. Metabolic demand for cholesterol (for synthesis of bile acids, steroids, or membranes) is met by increased synthesis

of LDL receptors, which promote endocytosis and release of free cholesterol.

- Apolipoproteins are protein constituents of lipoproteins. Apolipoprotein B is the main structural protein of LDL and VLDL. **High concentrations of apolipoprotein B are associated with an increased risk of coronary artery disease.**

- High-density lipoprotein (HDL) is involved in the transport of cholesterol from peripheral cells back to the liver. HDL absorbs free cholesterol released during cell turnover. This cholesterol is esterified by the enzyme *lecithin:cholesterol acyltransferase*, and the cholesterol esters are transferred to VLDL or IDL particles (Fig. 5.2.1).

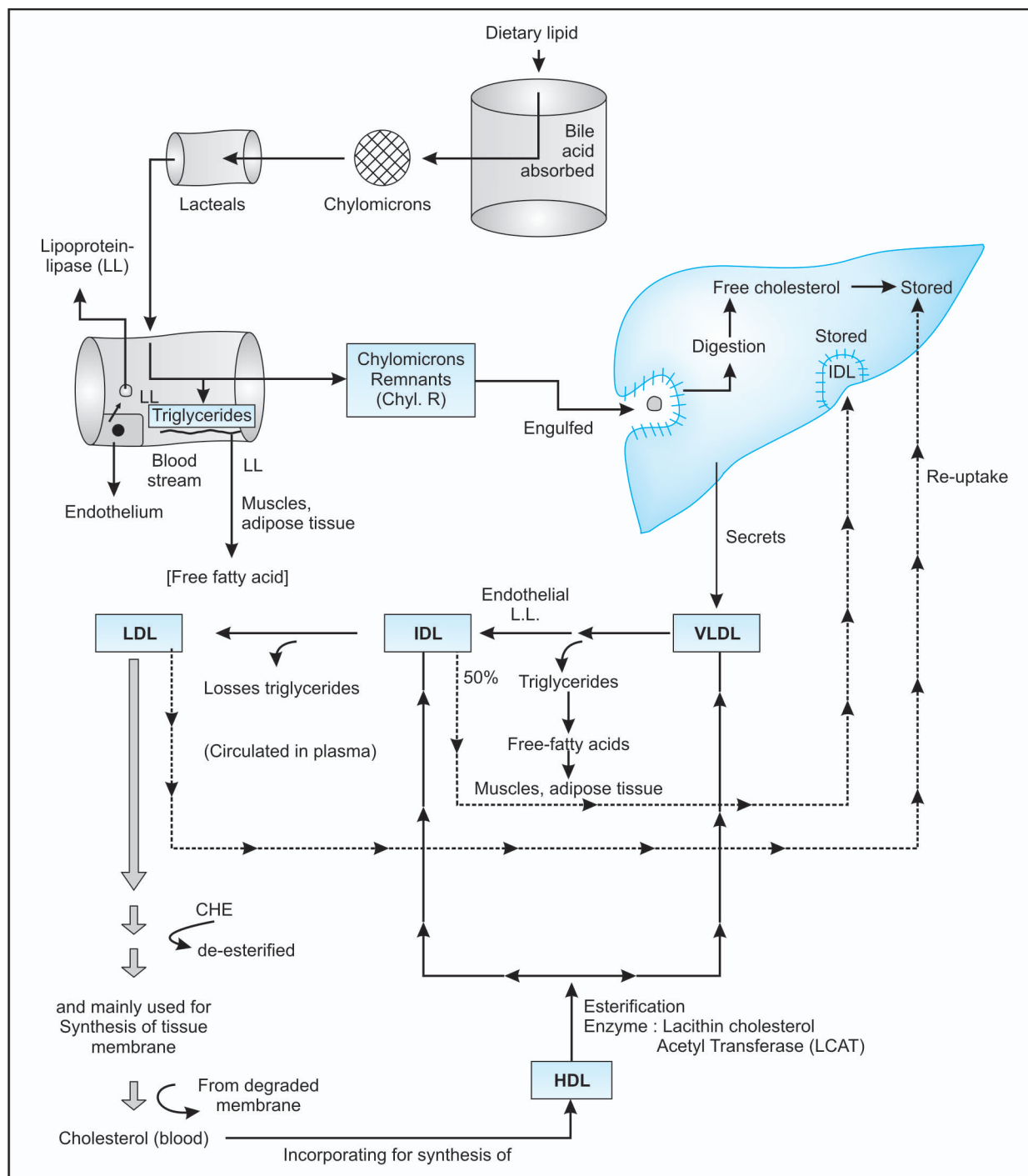


Fig. 5.2.1: Synthesis, storage and fate of various lipoproteins

Nonspecific pathways

- When plasma lipoprotein concentrations are high, macrophages and other scavenger cells take part in lipoprotein degradation.
- This leads to cholesterol deposits in macrophages or arterial walls (atheromas) and of tendons and skin (xanthomas).

Hyperlipoproteinemias

Definition: Hyperlipoproteinemias (HPL) are conditions in which the concentration of cholesterol or triglyceride (TG) carrying lipoproteins in the plasma is elevated above normal. Increase in lipoproteins can increase the development of atherosclerosis and is a risk factor for **Ischemic Heart Diseases like Myocardial infarction**.

Causes

- Primary hyperlipoproteinemias may be single-gene congenital defects or polygenic (multifactorial).
- Secondary hyperlipoproteinemia may occur in diabetes, hypothyroidism, alcoholism, biliary cirrhosis, or renal disease, or in women taking oral contraceptives.

Use of drug therapy

- In persons with hyperlipoproteinemia, lowering the serum lipid concentration reduces the risk of atherosclerosis and its consequences. Specifically, a reduction in plasma LDL can reduce the risk of coronary artery disease.
- Some types of hypertriglyceridemia can cause life-threatening pancreatitis. Reduction of serum lipids has been demonstrated to be beneficial.
- Drug therapy is usually tried after dietary fat restriction, reduction of atherosclerotic risk factors, and moderate exercise programs have failed to lower serum lipids to an acceptable level.
- Bile acid sequestrants, niacin, β -hydroxy- β -methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, and fibric acid derivatives demonstrably lower the risk of coronary artery disease; only **niacin** has been shown to reduce over all mortality.

HYPOLIPIDEMICS (ANTHYPERLIPIDEMIC AGENTS)

- HMG-CoA reductase inhibitors: Lovastatin, Simvastatin, Pravastatin
- Fibric acids : Gemfibrozil, Clofibrate, Fenofibrate
- Bile acid binding resins : Cholestyramine, Colestipol
- Antioxidant : Probucol
- Miscellaneous : Nicotinic acid, Neomycin.
- Ezetimibe : Intestinal

Bile Acid Sequestrants (Cholestyramine, Colestipol)**Mechanism of action and pharmacological effects**

- The loss of bile acids leads to an increased conversion of cholesterol into bile acids
- Cholestyramine and colestipol are resins that bind bile acids in the intestine, forming insoluble complexes, which are then excreted in the feces (Fig. 5.2.2).
- There is also a compensatory increase in hepatic LDL receptors.
- The net effect is reduction in serum LDL and cholesterol levels.

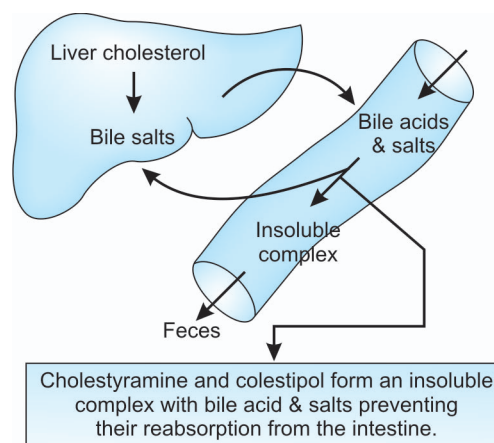


Fig. 5.2.2: Mechanism of bile acid binding resins

Therapeutic uses

- These agents are now also used to reduce elevated LDL levels.
- The earliest use of bile acid sequestrants was to control pruritus in patients with cholestasis and elevated plasma bile acids.
- The bile acid sequestrants are not effective for treating patients with elevated chylomicrons, VLDL, or IDL; in addition, these agents elevate triglyceride levels.
- Patients with heterozygous **familial hypercholesterolemia** or **polygenic hypercholesterolemia** can be expected to respond.

Adverse effects

- The most common untoward effects are gastrointestinal discomfort and constipation.
- Because bile acid sequestrants are not absorbed, they have no adverse systemic effects.
- The resins may cause or aggravate steatorrhea.
- These agents may bind other drugs (e.g., fat-soluble vitamins, chlorothiazide, anticoagulants, digitalis, glycosides), and impeding their absorption.

HMG-CoA Reductase Inhibitors (Lovastatin, Pravastatin, Simvastatin, Mevastatin)

Mechanism of action and pharmacological effects

- 3-HMG CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis.
- Drugs that inhibit HMG-CoA reductase are highly effective in lowering serum LDL-cholesterol levels (Fig. 5.2.3).
- These drugs reduce serum levels of LDL, LDL-cholesterol, VLDL-cholesterol and triglycerides.
 - a. The decrease in LDL appears to result from an increase in hepatic LDL receptors, which causes an increase in receptor-mediated clearance of LDL and IDL.
 - b. HDL-cholesterol is elevated.

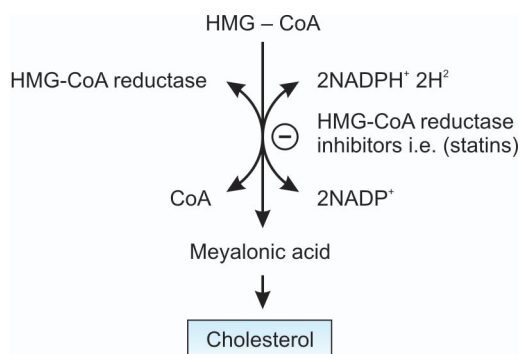


Fig. 5.2.3: Inhibition of HMG-CoA reductase

Therapeutic uses: HMG-CoA reductase inhibitors are:

1. Indicated for patients with hypercholesterolemia who are at high risk of myocardial infarction.
2. Useful in secondary hyperlipoproteinemia resulting from diabetes mellitus or nephrotic syndrome.
3. Useful in patients with combined elevated cholesterol and triglycerides.
4. Specifically indicated for types IIa and IIb hyperlipoproteinemia in which IDL and total cholesterol are elevated.

Adverse effects

- Serum hepatic transaminases are elevated in 2% of patients and muscle creatine phosphokinase levels are elevated in 11%.
- Gastrointestinal reactions include flatulence and diarrhea.
- Periodic slit-lamp examinations are suggested before and during therapy, because ocular opacities have been noted in dogs.

- When combined with another lipid-lowering drug or with cyclosporine, HMG-CoA reductase inhibitor therapy can cause myopathies, sometimes progressing to rhabdomyolysis and renal failure.

Niacin (Nicotinic acid): Mechanism of action and pharmacological effects

- In large doses, niacin reduces serum triglycerides by lowering VLDL, usually within 1-4 days (Fig. 5.2.4).
- Niacin usually produces a mild to moderate increase in HDL.
- The reduction of VLDL, in turn, reduces IDL and LDL.

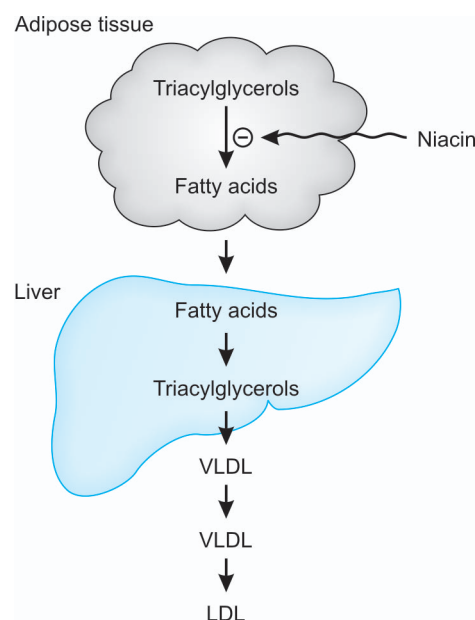


Fig. 5.2.4: Niacin inhibits lipolysis in adipose tissue

- Niacin does not significantly affect either total body production or biliary excretion of cholesterol.

Therapeutic uses

- Niacin is helpful in controlling a wide range of hyperlipidemias.
- It is particularly useful for type V hyperlipoproteinemia, characterized by severe hypertriglyceridemia and elevated chylomicrons.
- It is not useful in familial lipoprotein lipase deficiency.

Adverse effects

They can be minimized by taking the drug with meals and increasing the dosage gradually.

- Gastrointestinal distress is common, and peptic ulceration has occurred.

- Niacin produces prostaglandin-mediated intense flushing and itching.
- Glucose intolerance and hyperuricemia can occur.
- Hepatic dysfunction can occur with high-dose regimens.

Fibric Acid Derivatives (Clofibrate, Gemfibrozil)

Mechanism of action and pharmacological effects

- **The mechanism of action:** It has not yet been fully established, but it is known that fibric acid derivatives increase the activity of lipoprotein lipase, the enzyme that degrades chylomicrons and VLDL (Fig. 5.2.5).
- **Pharmacological effects:** The fibric acid derivatives decrease synthesis of apolipoprotein B and lower serum VLDL levels, thus reducing serum triglycerides.
- **With clofibrate:** The net effect on serum cholesterol in most patients is minimal. However, serum cholesterol is significantly reduced in patients with familial type III hyperlipoproteinemia. Clofibrate has no effect on chylomicron levels or on HDL levels.

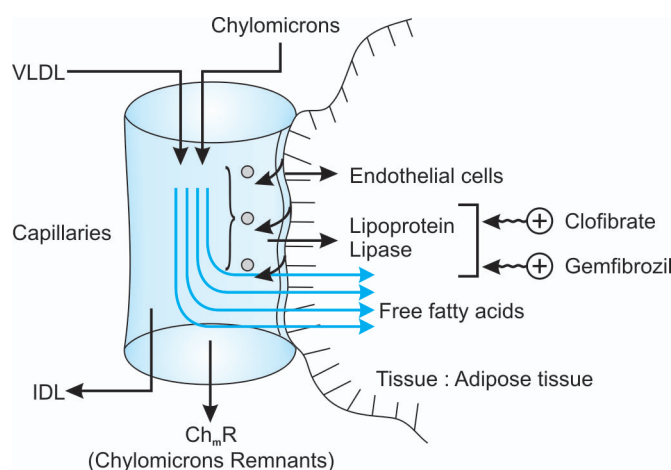


Fig. 5.2.5: Clofibrate and Gemfibrozil stimulates lipoprotein lipase activity

- **Gemfibrozil:** Lowers plasma VLDL-cholesterol levels, lowers LDL-cholesterol to a lesser degree, and raises HDL-cholesterol.

Therapeutic uses

- Fibric acid derivatives are indicated for patients with familial type III hyperlipoproteinemia, in which VLDL and IDL levels are increased.
- Gemfibrozil is also useful in type V hyperlipoproteinemia in which both chylomicron and triglyceride levels are increased.
- Gemfibrozil is useful for hypertriglyceridemia, whether or not accompanied by hypercholesterolemia.

- Neither clofibrate nor gemfibrozil is useful in type I hyperlipoproteinemia with elevated chylomicrons or triglycerides but normal VLDL levels.

Adverse effects

- Fibric acid derivatives are generally well tolerated.
- The most common unwanted effects are mild gastrointestinal reactions, including cholelithiasis.

Lipophilic Antioxidants (Probucol)

Mechanism of action and pharmacological effects.

The mechanism of action is unclear but appears to involve inhibition of the oxidation of LDL and reduction of its uptake by macrophages.

1. Effect on serum lipids:
 - a. Probucol reduces total serum cholesterol; it lowers HDL-cholesterol more than LDL-cholesterol.
 - b. Probucol has little or no effect on VLDL or triglycerides (Fig. 5.2.6).

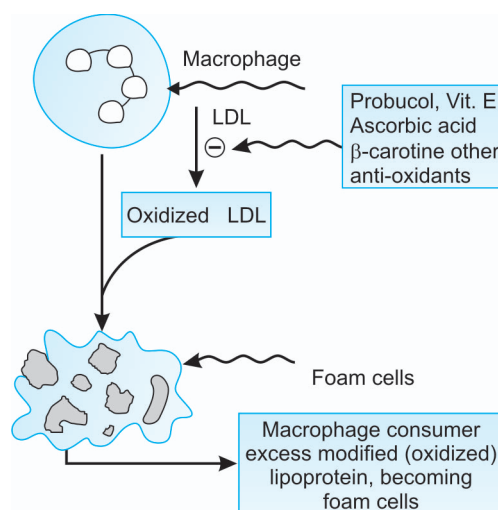


Fig. 5.2.6: Mechanism of action of probucol

2. Effect on cholesterol deposits:
 - a. Probucol induces marked regression of xanthomas.
 - b. In rabbits, a marked reduction in atheromatous deposits has been found.

Therapeutic uses: Probucol is generally combined with another type of lipid lowering drug for the treatment of general hypercholesterolemia.

Adverse effects

- Gastrointestinal reactions are the most common untoward effects.
- Probucol is stored in body tissue for up to 6 months.

Drugs Used in the Disorders of Coagulation

Hemostasis

It is a complex phenomenon in which there occur spontaneous arrest of bleeding from the damaged blood vessels. In the process, complex interactions take place between the injured vessel wall, platelets and clotting factors.

- Coagulation and fibrinolysis are in the state of dynamic equilibrium.
- Following injury, to a small blood vessel there occurs:
 1. Local vasoconstriction.
 2. Formation of a plug which temporarily stops bleeding (hemostatic plug) due to platelet adhesion and aggregation.
 3. This is reinforced by fibrin to form definitive clot for long-term hemostasis.
- Thrombosis is a pathological condition resulting from inappropriate activation of hemostatic mechanisms.
 - Venous thrombosis is usually associated with stasis of blood; a venous thrombus has a small platelet component and a large component of fibrin.
 - Arterial thrombosis is usually associated with atherosclerosis, and the thrombus has a large platelet component.
- **In arteries:** Platelets mass is the main constituent of the thrombus: **White/gray thrombus:** Therefore antiplatelets are preferred as antithrombotic agents.
- **In veins:** Fibrin (coagulant) plug is the main constituent of the thrombus: **Red thrombus:** Therefore anti-coagulants are preferred as antithrombotic agent.
- Clotting factors are proteins synthesized by the liver.
- A portion of a thrombus may break away, travel as an embolus and lodge downstream, causing ischemia and infarction.

The **cascade theory** consists of two systems: the extrinsic and the intrinsic system are involved in the process of coagulation (Fig. 5.3.1). Several proteins interact in a cascading series to form the clot.

a. **Intrinsic System** (inside the blood vessels): This system requires all factors which are present in blood and damaged platelets for coagulation. This process start on:

- *In vitro*: Contact of hageman (XII) factor with glass
- *In vivo*: Collagen/Kellikrenin

b. **Extrinsic System** (outside the blood vessel): This system is triggered by release of tissue thromboplastin, i.e. a protein – phospholipid mixture, that activate factor VII.

Factors for Coagulation

I	Fibrinogen	II	Prothrombin
III	Tissue Thromboplastin	IV	Ca ⁺⁺
V	Proaccelerine (labile)	VI	No factor
VII	Stable factor	VIII	AHF / AHG-A
IX	Christmas factor (AHF-B)	X	Stuart factor
XI	PTA (AHF-C)	XII	Hagmans factor
XIII	Fibrin stabilizing factor (lucky lorentz factor)		

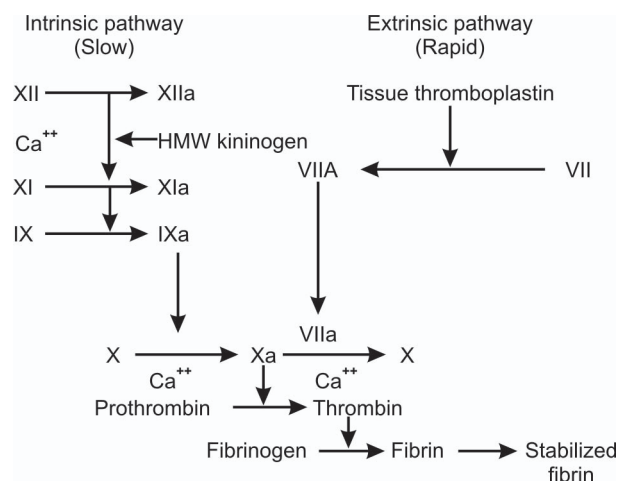


Fig. 5.3.1: Cascade of coagulation, via Intrinsic and Extrinsic pathways

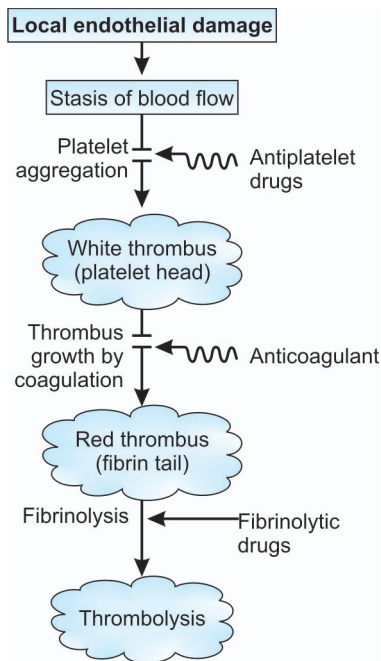


Fig. 5.3.2: Therapeutic application of antiplatelet, anticoagulant and fibrinolytic drugs in various phase of thrombus formation

Blood coagulation (fibrin formation): The clotting system consists of a cascade of proteolytic enzymes and co-factors.

- Inactive precursors are activated in series, each giving rise to more of the next.
- The last enzyme, thrombin, derived from prothrombin (II), converts soluble fibrinogen (I) to an insoluble mesh-work of fibrin in which blood cells are trapped, forming the clot.
- There are two pathways in the cascade:
 - The extrinsic pathway which operates *in vivo*
 - The intrinsic or contact pathway which operates *in vitro*.
- Both pathways result in activation of factor X, which then converts prothrombin to thrombin.
- Calcium and a negatively charged phospholipid (PL) are essential for three steps, namely for the actions of:
 - Factor IXa on X
 - Factor VIIa on X
 - Factor Xa on II.
- PL is provided by activated platelets adhering to the damaged vessel.
- Some factors promote coagulation by binding to PL and a serine protease factor, e.g. factor Va in the activation of II by Xa; VIIIa in the activation of X by IXa.

- Blood coagulation is controlled by:
 - Enzyme inhibitors, e.g. antithrombin III
 - Fibrinolysis (Fig. 5.3.1).

ANTICOAGULANTS

Definition: They are drugs that reduce the coagulability (ability to clot) of the blood (Fig. 5.3.2).

Classification

1. Anticoagulants used *in vitro* are Heparin, Citrates, Oxalates and Sodium edetate.
2. Anticoagulants used *in vivo* are:
 - a. Fast acting: Heparin, Heparinoids – Heparin sulphate, Dextran sulphate.
 - b. Slow acting: Oral anticoagulants.

Coumarin derivatives :	Bishydroxycoumarin, Warfarin sodium, Nicoumalone
Indandione derivatives:	Phenindione, Diphenadione

Heparin

- It was discovered by McLean, a medical student in 1916. It was named 'heparin' as it was first extracted from the liver (*hep*).
- Heparin is the strongest acid in the body. It is a mucopolysaccharide found in the mast cells of the liver, lungs and intestinal mucosa.

Actions: Heparin is a powerful anticoagulant (prevent coagulation) that acts instantaneously both *in vivo* (in the body) and *in vitro* (outside the body in test tube).

Mechanism of action

- Heparin activates plasma antithrombin III which binds to and inactivates the clotting factors.
- This is a physiological reaction, but heparin accelerates it by 1000 folds. Clotting time is prolonged.
- The heparin–antithrombin III complex inhibits activated factor X and thrombin, while low molecular weight (LMW) heparin only inhibits factor X and not thrombin.

Other actions: Heparin activates lipoprotein lipase which hydrolyses triglycerides present in the plasma and thus clears the plasma of lipids.

Pharmacokinetics

- Orally heparin is not effective.
- It is given IV or SC. It should not be given IM because it may cause hematomas.

- When given intravenously the onset of action is immediate, reaches peak in 5-10 minutes and clotting time returns to normal in 2-4 hours.
- Treatment is monitored by the APT (preferable) or clotting time.
- Heparin is metabolized by heparinase in the liver.

Dose: Heparin is given as a bolus dose of 5000 units followed by a maintenance dose of 1000 units/hour as infusion.

Adverse reactions

- Bleeding is the most common, major adverse effect of heparin.
- Thrombocytopenia: Heparin introduced platelet—aggregation and formation of antiplatelet and antibodies both result in thrombocytopenia.
- Hypersensitivity reactions: For commercial use heparin is obtained from bovine lung or porcine intestine. Because of its animal origin allergic reactions are quite common.
- Alopecia is reversible.
- Osteoporosis – on long-term use.

Contraindications to Heparin Therapy: Bleeding disorders, intracranial hemorrhage, thrombocytopenia, hemophilia, severe hypertension, cirrhosis, ulcers in the gut, renal failure and neurosurgery.

Low Molecular Weight (LMW) Heparins, e.g. Enoxaparin, Dalteparin.

- Several LMW heparins (MW 2000-9000) are claimed to have equal efficacy, better bioavailability following SC injection and longer action as well as lower risk of bleeding in comparison to standard heparin preparations.
- They are used for the prevention and treatment of deep vein thrombosis and to maintain the potency of tubes in dialysis patients.

Heparin Antagonist

- Heparin antagonist is needed in severe heparin overdose, to arrest its anticoagulant effects.
- **Protamine sulphate** is a protein obtained from the sperm of certain fish. Given intravenously, it neutralizes heparin (1 mg for every 100 units of heparin).
- In the absence of heparin, protamine sulphate can itself act as a weak anticoagulant. Hence, overdose should be avoided.
- Protamine sulphate is a strongly basic protein which binds with the strongly acidic groups of heparin forming a stable complex which is devoid of anticoagulant activity.

Hirudin

- It is the anticoagulant found in **leeches**. It is a powerful thrombin inhibitor.
- It is produced by recombinant DNA technology and is being investigated in clinical trials.

ORAL ANTICOAGULANTS

- Cattle that were fed on spoiled sweet clover hay, developed a hemorrhagic disease in North America in 1924.
- This turned out to be due to bishydroxycoumarin, an anticoagulant in the spoiled sweet clover. Many related compounds were then developed and are also being used as rat poison.

Mechanism of action

- **Warfarin** and its congeners act as anticoagulants only *in vivo* because they act by interfering with the synthesis of vitamin K dependent clotting factors in the liver.
- They block the carboxylation of glutamate residues in prothrombin, factors VIII, IX and X. Carboxylation is necessary for these factors to participate in coagulation.

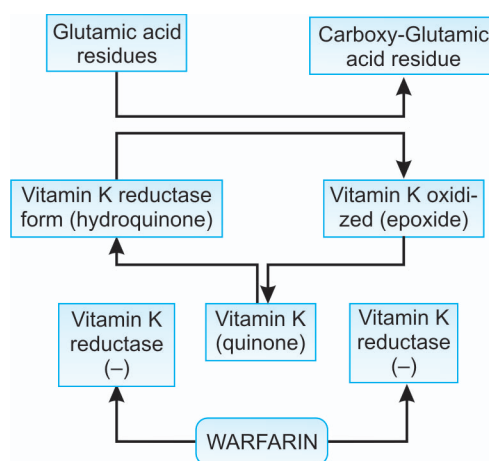


Fig. 5.3.3: Mechanism of vitamin K and warfarin

- The onset of action is slow; it develops over 1-3 days because oral anticoagulants do not destroy the already circulating clotting factors.
- Prothrombin time (PT) is measured to monitor the treatment. It takes 5-7 days for PT to return to normal after stopping oral anticoagulants (Fig. 5.3.3).

Pharmacokinetics: Warfarin, if taken orally, completely absorbed and is 99% bound to plasma proteins.

Adverse effects

- Hemorrhage is the main hazard. Bleeding in the intestines or brain can be life threatening in someone. Minor

episodes of epistaxis and bleeding gums are common. Treatment – depends on the severity:

- Stop the anticoagulant.
 - Fresh blood transfusion is given to supply clotting factors.
 - Antidote:** The specific antidote is vitamin K₁ oxide. It allows synthesis of clotting factors, but even on IV administration, the response to vitamin K₁ oxide needs several hours. Hence in emergency, fresh whole blood is necessary to counter the effects of oral anticoagulants.
- Other adverse effects include allergic reactions, gastrointestinal disturbances and teratogenicity.

Factors Influencing Oral Anticoagulant Activity

Factors enhancing activity

Poor diet, bowel disease, liver disease and chronic alcoholism—result in vitamin K deficiency

Factors reducing activity

Pregnancy—there is increased synthesis of clotting factors
Hypothyroidism—there is reduced degradation of clotting factors.

Drug Interactions

Many drugs potentiate warfarin action:

- Drugs that displace warfarin from plasma protein binding sites like NSAIDs enhance its plasma levels.
- Drugs that inhibit platelet function: NSAIDs like aspirin increase the risk of bleeding.
- Drugs like broad spectrum antibiotics inhibit gut flora thus decreasing vitamin K synthesis.
- Drugs that inhibit hepatic drug metabolism like cimetidine, chloramphenicol and metronidazole enhance plasma levels of warfarin.

Some drugs reduce the effect of oral anticoagulants

- Drugs that enhance the metabolism of oral anticoagulants—microsomal enzyme inducers like barbiturates, rifampicin, griseofulvin enhance the metabolism of oral anticoagulants. When these drugs are suddenly withdrawn, excess anticoagulant activity may result in hemorrhages.
- Drugs that increase the synthesis of clotting factors—oral contraceptives.

Uses of Anticoagulants

- Venous thrombosis and pulmonary embolism—anticoagulants prevent extension of thrombus and recurrence of embolism.

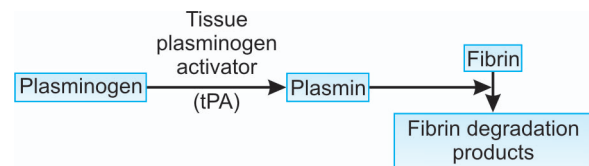
- Postoperative, post-stroke patients; bedridden patients due to leg fractures and other causes—who cannot be ambulant for several months – anticoagulants prevent venous thrombosis and pulmonary embolism in such patients.
- Rheumatic valvular disease – anticoagulants prevent embolism.
- Unstable angina – heparin reduces the risk of myocardial infarction in patients with unstable angina.
- Vascular surgery, artificial heart valves and hemodialysis—anticoagulants prevent thromboembolism.

Contraindications to Anticoagulant Therapy

- Bleeding disorders including thrombocytopenia
- Severe hypertension
- Malignancies
- Bacterial endocarditis
- Liver and kidney diseases.

THROMBOLYTICS OR ANTITHROMBOTIC AGENTS (FIBRINOLYTICS)

Antithrombotic agents are those agents that prevent or reduce the formation of arterial platelet thrombi. Thrombolytics lyse (dissolve) the clot or thrombi by activating the natural fibrinolytic system.



- Plasminogen circulates in the plasma and also some of it is bound to fibrin.
- Tissue plasminogen activator (tPA) activates plasminogen which is converted to plasmin.
- Plasmin degrades fibrin thereby dissolving the clot.
- Thrombolytic agents [e.g., **streptokinase, anistreplase (eminase), recombinant tissue type plasminogen activator (tPA), and urokinase**] are used in acute, extensive thromboembolic disease, acting via the conversion of endogenous plasminogen to plasmin, a protease. The newly formed plasmin hydrolyzes fibrin in hemostatic plugs and degrades fibrinogen and Factors V and VII (Fig. 5.3.4).
 - Thrombotic coronary artery occlusion occurs in more than 80% of patients with acute transmural myocardial infarction. Recent data suggest that, when administered to patients after myocardial infarction, *tPA produces a greater reduction of mortality rates than streptokinase.*

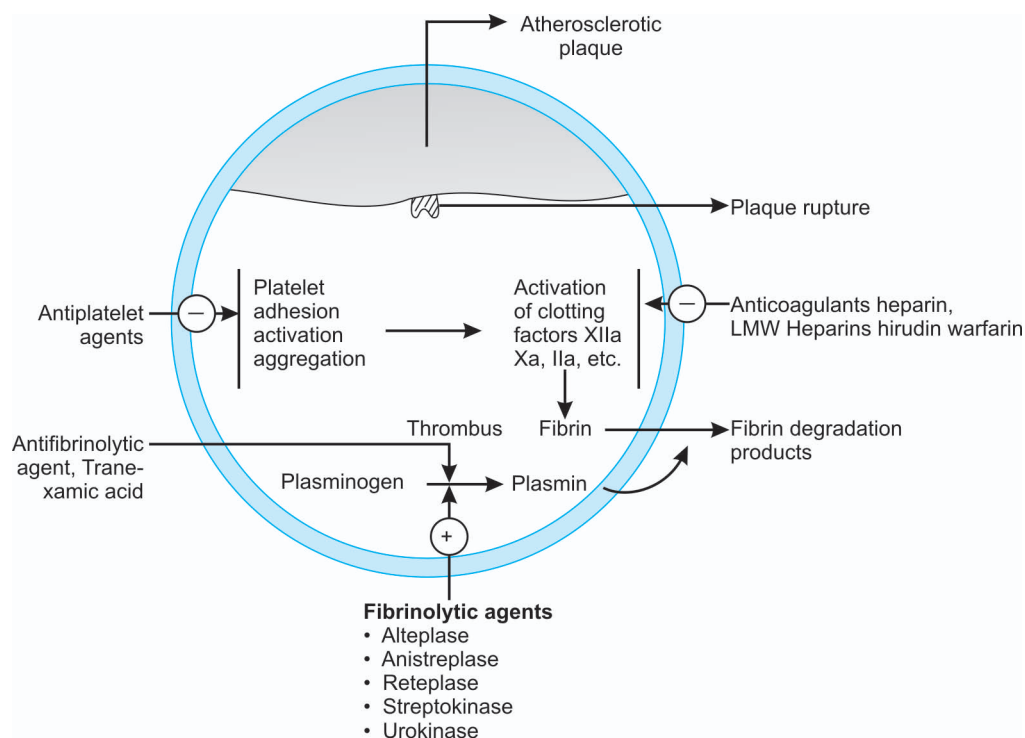


Fig. 5.3.4: Fibrinolytic system

2. The use of thrombolytic agents is contraindicated in the presence of recent stroke, craniotomy, head trauma, or brain tumor.

Preparations

Streptokinase: It is a purified preparation of a bacterial protein elaborated by group C β -hemolytic streptococci.

- Streptokinase produces an activator complex that converts plasminogen to plasmin. The half-life of the activator complex is 80 minutes. The mechanism of elimination is unknown. The complex is inactivated in part by antistreptococcal antibodies.
- Streptokinase decreases fibrinogen levels for 24-36 hours. Plasma and blood viscosity and red blood cell aggregation are decreased.

Therapeutic uses: The primary use of streptokinase is for the management of acute myocardial infarction resulting from intracoronary thrombi. Fibrinolytics may be administered intravenously or by the intracoronary route.

Adverse effects

1. Systemic bleeding, particularly intracranial hemorrhage, occurs in 1% of patients. Gastrointestinal bleeding occurs in 5-10% of patients.
2. Hypotension may occur.

3. Allergic reactions, ranging from minor bronchospasm to anaphylactic reactions, are common.
4. Reperfusion atrial or ventricular dysrhythmias may occur.

Anistreplase (eminase): It is a plasminogen activator approved for the intravenous treatment of coronary thrombosis. Anistreplase is an acylated inactive complex of streptokinase and human lys-plasminogen.

- Anistreplase has a half-life of 90 minutes. It does not require a prolonged infusion.
- After injection, the acyl group slowly hydrolyses, producing an activator that converts plasminogen to plasmin, initiating fibrinolysis.

Therapeutic uses: Management of acute myocardial infarction consists of the intravenous administration of anistreplase to lyse intracoronary thrombi. Intravenous administration is more convenient because it does not require prolonged infusion.

Adverse effects

- Bolus injections may produce systemic bleeding and hematoma formation at the catheter entry site, intracranial hemorrhage, and gastrointestinal bleeding.
- Hypotension, allergic reactions, and reperfusion dysrhythmias have been reported.

tPA [Recombinant tissue type plasminogen activator] or Alteplase: It is a commercial formulation of a naturally occurring thrombolytic enzyme.

- tPA is rapidly metabolized in the liver and excreted in the urine. The half-life is only 5 minutes.
- tPA selectively promotes the conversion of plasminogen to plasmin in the presence of fibrin. tPA binds to fibrin and activates bound plasminogen several hundred times more rapidly than circulating plasminogen.

Therapeutic uses and administration

- Management of acute myocardial infarction resulting from intracoronary thrombi is the primary use of tPA.
- Heparin is generally given with tPA to maintain potency of catheters and prevent reocclusions of coronary arteries.

Adverse effects: Bleeding complications include: Hematomas at the catheterization site, Intracranial hemorrhage, Gastrointestinal bleeding, Serious allergic reactions and reperfusion dysrhythmias have been reported.

Urokinase: It is an enzyme produced by the kidney and found in the urine.

- Urokinase is administered intravenously and is cleared rapidly by the liver. The half-life is 20 minutes.
- Urokinase converts endogenous plasminogen to the enzyme plasmin, which degrades fibrin clots, fibrinogen, and other plasma proteins.

Therapeutic uses

- Urokinase is used in cases of acute massive pulmonary emboli.
- Urokinase is used to restore potency to intravenous catheters.
- Urokinase is used in cases of acute thrombi obstructing coronary arteries.

Adverse effects: Systemic bleeding, similar to that which occurs with use of streptokinase, Allergic reactions are usually mild and rare and fever occurs in 2-3% of treated patients.

Contraindications to thrombolytic therapy

- Recent surgery, injury, gastrointestinal bleeding, stroke
- Severe hypertension
- Bleeding disorders.

ANTIFIBRINOLYTICS

Antifibrinolytics inhibit plasminogen activation and thus prevent fibrinolysis.

Epsilon aminocaproic acid (EACA) and its analogue tranexamic acid are antifibrinolytics.

- They are used in overdose of fibrinolytics, and to reduce bleeding after prostatic surgery or after tooth extraction in hemophiliacs – but the beneficial effect is uncertain.

Other Drugs Affecting Blood Flow

Pentoxifylline, a methylxanthine derivative

It is used for the treatment of intermittent claudication resulting from occlusive arterial disease

- **Pentoxifylline** is thought to increase the flexibility of erythrocytes, thereby easing their passage through the capillary microcirculation. Serum fibrinogen is also reduced, and platelet aggregation is inhibited.
- Pentoxifylline is metabolized by the liver and is excreted by the kidney within 24 hours after an oral dose. Adverse effects include minor nausea, dizziness, and headache.

Danazol: It is a synthetic androgen, has been found to increase serum concentrations of clotting Factors VIII and IX, but long-term use in the treatment of hemophilias A and B has not proved efficacious.

- However, danazol has been associated with a rise in platelet count in patients with idiopathic thrombocytopenic purpura and with a rise in serum α_1 -antitrypsin activity in those with α_1 -antitrypsin deficiency.

ANTIPLATELET DRUGS

- Healthy vascular endothelium prevents platelet adhesion.
- Platelets adhere to diseased or damaged areas and become activated, i.e. they change shape, exposing negatively charged phospholipids and GPII_b/III_a receptors and synthesize and release various mediators, e.g. TXA₂, ADP, which stimulate other platelets to aggregate.
- Aggregation entails links formed by fibrinogen binding to the GPII_b/III_a receptors on adjacent constitute the localizing focus for fibrin formation.
- The activated platelets constitute the localizing focus for fibrin formation.
- Chemotactic factors and growth factors necessary for repair, but also implicated in atherogenesis, are released.
- Platelets form the initial hemostatic plug at the site of vascular injury and are also involved in the formation of atherosclerosis. By inhibiting the platelet function, thrombosis and atherosclerotic vascular disease can be largely prevented.
- Antiplatelet drugs or drugs interfering with platelet function are aspirin, dipyridamole, sulphinpyrazone and ticlopidine.

Aspirin: Aspirin in low doses (75 mg / day) inhibits cyclo-oxygenase (COX) irreversibly. The balance between prostacyclin (an inhibitor of aggregation generated by vascular endothelium) and TXA₂ (a stimulant of aggregation generated by platelets) is thus altered, since the endothelium can synthesize more enzyme but platelets cannot, TXA₂ synthesis only recovers when new platelets are formed.

Dipyridamole

- It is a phosphodiesterase inhibitor which interferes with platelet function by increasing platelet cyclic AMP levels. It is used for the prophylaxis of thromboemboli in patients with prosthetic heart valves.
- Other clinically available antiplatelet drugs include: **Epoprostenol (synthetic prostacyclin), Ticlopidine and Clopidogrel** (which inhibit expression of GPII_b/III_a receptors in response to ADP) and a monoclonal antibody against the GPII_b/III_a receptor (abciximab). Drugs being tested include agents that either inhibit TXA₂ synthesis or block TXA₂ receptors or have both actions.
- Adverse effects include dyspepsia, diarrhea, bleeding and leukopenia. It is used in patients who cannot tolerate aspirin.

Clinical use of antiplatelet drugs: The main drug is aspirin. Uses mainly related to arterial thrombosis, and include:

- Acute myocardial infarction
- High-risk of myocardial infarction, including:
 - Patients who have recovered from myocardial infarction.
 - Patients with symptoms of atherosclerosis, including angina, transient cerebral ischemic attacks, intermittent claudication.
- Following coronary artery bypass grafting
- Following coronary artery angioplasty and stenting; (either ticlopidine or abciximab are used in some patients in addition to aspirin)
- Acute thrombotic stroke
- Atrial fibrillation in patients who have a contraindication to oral anticoagulation.
- Other antiplatelet drugs (e.g. poprostenol, dipyridamole) have limited clinical applications.

COAGULANTS

Definition: These are drugs that promote coagulation (procoagulants) and control bleeding.

- They are also called hemostatics. They may be locally acting or systemically acting.

COAGULANTS USED LOCALLY

- Local hemostatics are called **styptics**.
- Physical methods like application of pressure, tourniquate or ice can control bleeding.

Styptics are local hemostatics that are used on bleeding sites. In dental practice they are used to stop bleeding at tooth socket, etc.

They are of following types:

1. **Adrenaline:** Sterile cotton soaked in 1:10,000 solution of adrenaline is commonly used as nasal packs for stopping epistaxis and to control bleeding in tooth sockets. Adrenaline stops bleeding by vasoconstriction.
2. **Thrombin powder:** It is sprinkled over the bleeding surface following skin grafting. It is obtained from bovine plasma.
3. **Gelatin foam:** It is porous spongy gelatin used with thrombin to control bleeding from wounds. It gets completely absorbed within 1-2 months and can be left in place after suturing of the wound.
4. **Fibrin:** It is obtained from human plasma and is used for covering or packing bleeding surfaces. It is available as sheets.
5. **Astringents:** Like tannic acid (20% in glycerine) are used on bleeding gums for controlling bleeding.
6. **Thromboplastin powder:** It is used in surgery as a *styptic*.

COAGULANTS USED SYSTEMICALLY

Vitamin K

- Along with vitamin A, D and E, vitamin K is a fat-soluble vitamin which is essential for the biosynthesis of clotting factors.
- Vitamin K is of three types
 1. Vitamin K₁: *Phylloquinone*; It is present in food (obtained from plant sources).
 2. Vitamin K₂: *Menaquinones*; It is produced in the intestine by bacteria.
 3. Vitamin K₃: *Menadione*; It is a synthetic compound used therapeutically.

Pharmacology of Vitamin K

- Vitamin K is essential for the biosynthesis of clotting factors; prothrombin and factors VII, IX and X by the liver.
- The reduced form of vitamin K is a cofactor in the post-translational γ-carboxylation of a cluster of glutamic acid (glu) residues in each of factors II, VII, IX and X; vitamin K is oxidized during the reaction. The γ-carboxylated glutamic acid (glu) residues are essential

for the interaction of these factors with Ca^{2+} and negatively charged phospholipid.

- Vitamin K deficiency results from liver diseases, malabsorption syndrome, long-term antibiotic therapy and very rarely by dietary deficiency.
- Dietary sources: Green leafy vegetables: spinach, cabbage; and cheese, liver, etc.
- Daily requirement: 50 to 100 microgram/day.
- Vitamin K deficiency is manifested as bleeding tendencies.

Clinical use of vitamin K: The treatment and/or prevention of:

- Bleeding due to oral anticoagulant drugs (e.g. warfarin)
- Hemorrhagic disease of the newborn
- Vitamin K deficiencies :
 - Tropical sprue, celiac disease, steatorrhea
 - Lack of bile (e.g. with obstructive jaundice).

Adverse effects: Adverse reactions are seen only on rapid parenteral administration: allergic reactions and jaundice can occur.

OTHER COAGULANTS

- Fresh plasma or whole blood is useful in most coagulation disorders as it contains all the clotting factors.
- Other concentrated plasma fractions like
 1. Fibrinogen,
 2. Antihemophilic factors VIII, II, VII, IX and X
 3. Adrenochrome monosemicarbazone
 4. Rutin (plant glycoside) and Ethamsylate are the various available coagulants for the treatment of specific deficiencies.
- **Viper russel snake venoms:** Some venoms like Viper russels venom stimulate thrombokinase and promote coagulation.



S E C T I O N

6

Excretory System

Diuretic Agents

INTRODUCTION

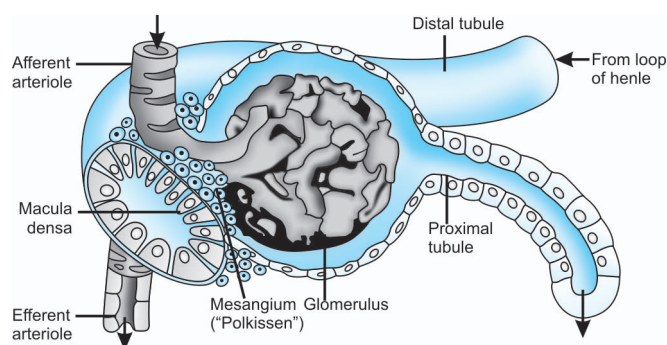


Fig. 6.1.1: Juxtaglomerular apparatus

- Besides the lung, the skin and the intestines, the kidneys are the most important excretory organs within the human body. It is the most important Homeostatic organ of the body.
- The kidneys control the salt and mineral contents, regulate the fluid balance and thus participate in the acid and base balance of the body. The main function of the kidneys is to maintain the balance of the normal composition of the blood and all other body fluids.
- Through the blood, all cell metabolic waste products are transported to the kidneys, where they are then filtered out of the blood plasma and passed out of the body.
- Excretion takes place through the urine. It is produced in the nephrons, functional unit of kidney of which over a million are to be found in the kidneys. Following several filtrations at different points, the urine eventually leaves the body via the ureter, the bladder and the urethra.

PHYSIOLOGY OF URINE FORMATION

Nephron: According to their function and structure, two parts of the nephron are distinguished:

- Renal corpuscle or malpighian body (*corpusculum renal*).
- Urinerous tubule or renal tubule (*tubulus renalis*).

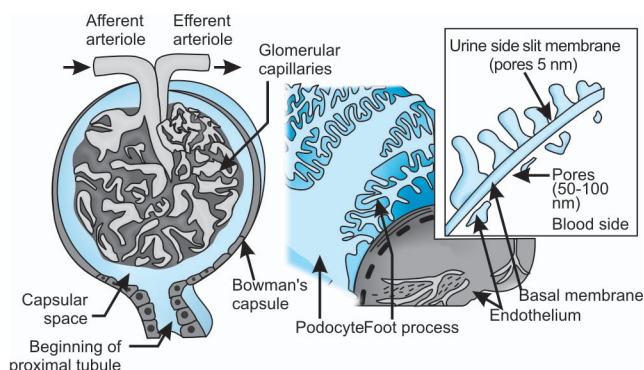


Fig. 6.1.2: Glomerulus and Bowman's capsule

- An aggregation of very fine capillaries (*glomerulum*) is enclosed by a watertight capsule (*capsula glomeruli* or Bowman's capsule) (Fig. 6.1.1).
- In the glomerulus the blood is filtered through pores of the vessels and cell clefts into the Bowman's capsule (Fig. 6.1.2). Very less substances, such as minerals, urea, creatinine (a metabolic product of the muscle tissues) and glucose, pass through the filter. The kidney receives about 25% of total CO.
- Blood cells and protein molecules are too big for the openings of the filter and remain in the blood. When, for example, due to infections, the openings of the filter extend, these substances get in the filtrate and can be detected in the urine.
- The filtered fluid, the primary urine, is collected by the Bowman's capsule and conducted to the adjacent urinerous tubules. 125 ml (0.03 gal) of primary urine are produced per minute which makes 170-180 (37.4-39.6 gal) liters in 24 hours.
- The urinerous tubules, also called renal tubules, extend from the renal cortex into the renal medulla. It is their task to recover those substances dissolved in the primary urine that are indispensable to the body (*reabsorption*).

- The renal tubules first proceed in a loop-like fashion and then pass down, up, and downwards again. Due to different morphological structures, the individual sections (main tubule, descending limb, middle piece and collecting tubule) take over different tasks in the *reabsorption* process.

Proximal tubule: Sodium bicarbonate, sodium chloride, amino acids and glucose are re-absorbed in the proximal tubule along with water by specific transport mechanisms. Osmotic diuretics act here.

Henle's loop: In the thin descending limb of the loop of Henle, Water is reabsorbed by osmotic forces. Hence osmotic diuretics are acting here too. The thick ascending limb actively reabsorbs sodium chloride from the lumen (but is impermeable to water) by $\text{Na}^+/\text{K}^+ / 2\text{Cl}^-$ co-transporter. 'Loop diuretics' selectively block this transporter (Fig. 6.1.3).

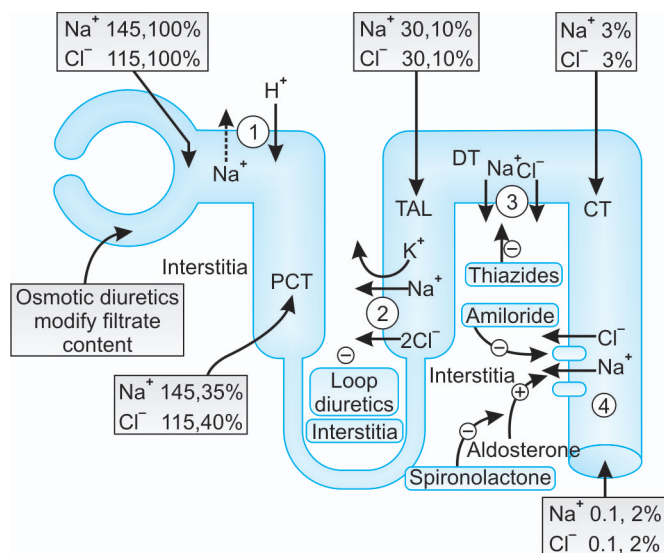


Fig. 6.1.3: Renal tubule showing various sites of action for different diuretic drugs

Distal convoluted tubule: In the early distal tubule, sodium chloride is reabsorbed by an electrically neutral Na^+ and Cl^- transporter. This transporter is blocked by thiazide diuretics.

Collecting tubule: In the late distal tubule and collecting duct, NaCl is actively reabsorbed, in exchange for K^+ and H^+ to maintain the ionic balance-regulated by aldosterone. Absorption of water is under the control of antidiuretic hormone (ADH).

- The resorption of substances is a complicated procedure accomplished, on the one hand, under the influence of physical processes and on the other, hormonally, controlled by the endocrine system.

- Everyday 99% of primary urine is reabsorbed. Thus, within 24 hours approximately 1.5 liters (0.33 gal) of urine are produced that are excreted by the body. The quantity of urine varies according to the external influences like the intake of fluids and physical stress.

• **Natriuresis:** Increase in renal sodium excretion.

• **Salturesis:** Increase in renal salt excretion.

DIURETICS

Diuretic is an agent which increases urine and solute excretion.

Classification

- Ceiling or high efficacy diuretics: Furosemide, Ethacrynic acid, Bumetanide, Piretanide, Torsemide.
- Moderate efficacy diuretics:
 - Thiazides diuretics:** Benzothiadiazines like Chlorothiazide, Hydrochlorothiazide, Polythiazide.
 - Thiazide related agents:** Clopamide, Indapamide, Chlorthalidone, Metolazone, Xipamide.
- Low efficacy diuretics:
 - Carbonic anhydrase inhibitors:** Acetazolamide.
 - Potassium sparing diuretics:** Triamterene, Amiloride, Spironolactone.
 - Osmotic diuretics:** Mannitol, Urea, isosorbide, Glycerol.
 - Methylxanthines:** Theophylline.

High Ceiling or Loop Diuretics

Furosemide (Furosemide): It is a sulfonamide derivative. It is the most popular loop diuretic (Fig. 6.1.4). Given intravenously it acts in 2-5 minutes, while following oral use, it takes 20-40 minutes; duration of action is 3-6 hours.

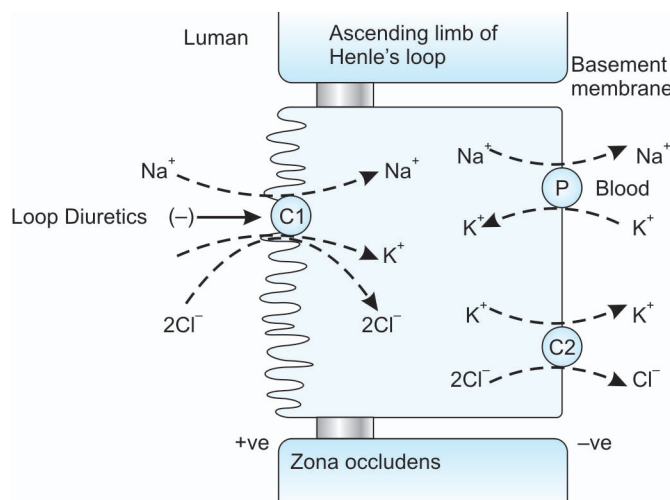


Fig. 6.1.4: Site and mechanism of action of loop diuretics

Mechanism of Action

- **Inhibition of electrolyte absorption:** Loop diuretics inhibit electrolyte reabsorption (Na^+ , K^+ , 2Cl^- , and co-transport mechanism) in the thick ascending limb of the loop of Henle. (that's why they are called loop diuretics) Because they act at the luminal surface of the nephron, they must reach the urine to exert a diuretic effect.
- **Inhibition of carbonic anhydrase**
 - a. Furosemide, bumetanide, and tolosemide are weak inhibitors of carbonic anhydrase, probably as a result of the substituted sulfonamide side chain.
 - b. Ethacrynic acid lacks a sulfonamyl group and does not inhibit carbonic anhydrase.

Pharmacological Effects

- Cl^- excretion is greater than Na^+ excretion. Hypochloramic alkalosis can occur, but it does not produce a refractory state.
- These diuretics increase renal blood flow without increasing the glomerular filtration rate.
- Large doses inhibit uric acid excretion (Secretion) therefore may induce gout.
- Loop diuretics also enhance the excretion of K^+ , Ca^{++} , and Mg^{++} (But Ca^{++} is reabsorbed in the distal tubule hence no hypocalcemia).
- They also alter renal hemodynamics to reduce fluid and electrolyte reabsorption in the proximal tubule.
- IV furosemide relieves pulmonary congestion and reduces left ventricular filling pressure by causing venodilation in congestive heart failure.

Pharmacokinetics

- **Furosemide, bumetanide, and tolosemide** are usually administered orally in a single dose once or twice daily. Both also can be administered intramuscularly or (more frequently) intravenously. Oral bioavailability is about 60-80%. $T_{1/2} = 1-2$ hrs.
- **Ethacrynic acid** is administered orally or intravenously once or twice daily. One of the main differences between furosemide and ethacrynic acid is that the former has a broader dose-response curve, i.e. DRC of ethacrynic acid is steeper.

Therapeutic Uses

1. **Edema:** Furosemide is highly effective for the relief of edema of all origins like cardiac, hepatic, pulmonary and renal edema.
 - Acute pulmonary edema is relieved by IV furosemide due to its immediate vasodilator effect and then by diuretic action, e.g. LVF (acute) following MI.

- In cerebral edema, frusemide is used as alternative to osmotic diuretics.
2. **Forced diuresis:** In poisoning due to drugs like barbiturates and salicylates, frusemide is used with IV fluids.
 3. **Hypertension:** With renal impairment may be treated with loop diuretics.
 4. **Hypercalcemia and hyperkalemia:** Loop diuretics enhance excretion of Ca^{++} and K^+ . But Na^+ and Cl^- should be replaced to avoid hyponatremia and hypochloremia.

Adverse Effects of Loop Diuretics

- **GIT disturbances** like nausea, vomiting and diarrhea are common with ethacrynic acid.
- **Hypokalemia and metabolic alkalosis** is dose dependent and can be corrected by K^+ replacement and correction of hypokalemia.
- **Hyperuricemia** may precipitate acute attacks of gout.
- **Hypocalcemia and hypomagnesemia** After prolonged use this may result in osteoporosis.
- **Hyponatremia, dehydration and hypovolemia** should be treated with saline infusion.
- **Hyperglycemia and hyperlipidemia** are mild in therapeutic doses.
- **Ototoxicity:** Loop diuretics cause hearing loss by a toxic effect on the hair cells in the internal ear—more common with ethacrynic acid. It is dose-related and generally reversible. Concurrent use of other ototoxic drugs should be avoided.
- **Allergic reaction** like skin rashes are more common with sulfonamide derivatives.

Thiazides and Thiazide-like Diuretics

Chemistry: All thiazides have a sulfonamide group. Chlorthiazide was the first thiazide to be synthesized.

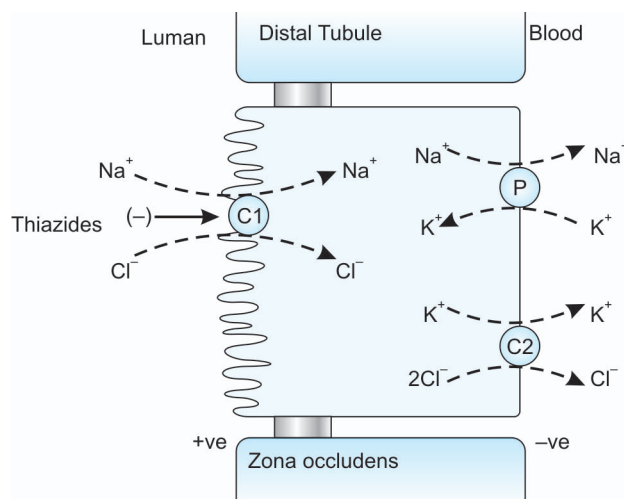


Fig. 6.1.5: Site and mechanism of action of thiazides

Mechanism of actions (Fig. 6.1.5)

- This group of drugs block Na^+/Cl^- co-transport in the early distal tubule (site 3).
- They also inhibit carbonic anhydrase activity. Increase in dose does not increase the response.
- Thiazides also enhance excretion of Mg^{2+} and K^+ (in distal segments, Na^+ in the lumen is exchange for K^+ which is then excreted).
- But they also inhibit urinary excretion of Ca^{2+} and uric acid.

Pharmacokinetics: Thiazides are well-absorbed orally and are rapid acting. Duration varies from 6-48 hours. They are excreted by the kidney.

Therapeutic uses

1. *Hypertension:* Thiazides are first line drugs.
2. *Edema:* Thiazides may be tried in hepatic or renal edema.
3. *Congestive heart failure:* Thiazides are the first line drugs in the management of edema due to mild to moderate CHF.
4. *Renal stones:* Hypercalciuria with renal stones can be treated with thiazides which reduce calcium excretion.
5. *Diabetes insipidus:* Thiazides reduce plasma volume and GFR and benefit such patients.

Adverse effects

- Hypokalemia, metabolic alkalosis, hyperuricemia, hypovolemia, dehydration, hyponatremia, hypercalcemia, and hyperlipidemia are similar to that seen with loop diuretics.
- Hyperglycemia induced by thiazides may precipitate diabetes mellitus probably by inhibition of insulin secretion. It is more common when long-acting thiazides are used for a long time.
- Weakness, fatigue and allergic reactions like rashes and photosensitivity can be seen.

Potassium Sparing Diuretics: Spironolactone**Mechanism of action**

- Spironolactone, a competitive antagonist of the mineralocorticoid aldosterone, interferes with aldosterone-mediated Na^+/K^+ exchange, increasing Na^+ loss at the distal tubular site while decreasing K^+ loss (Fig. 6.1.6).
- It is most effective when circulating aldosterone levels are high.

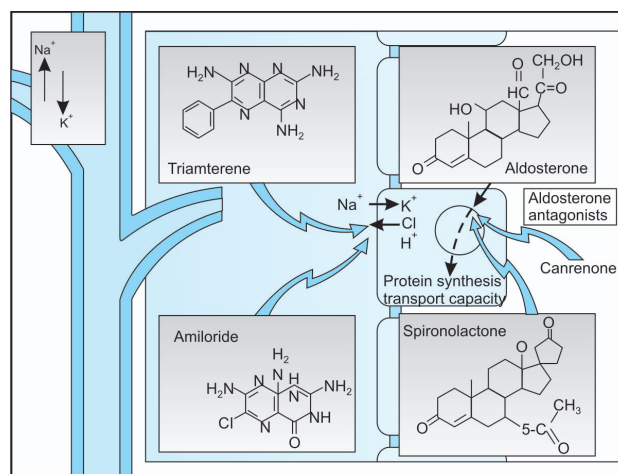


Fig. 6.1.6: Potassium sparing diuretics

Route of administration

- Spironolactone is usually given orally four times daily.

Therapeutic uses

- Spironolactone is often used as an adjunct to other diuretics to reduce the loss of K^+ in the management of refractory edema, such as that associated with Laennec's cirrhosis.
- It also used when adrenal gland tumors result in increased aldosterone levels.
- It can be used for edema resulting from congestive heart failure, although other diuretic agents are more effective.

Adverse effects

- Hyperkalemia can occur or be exacerbated, especially in patients with impaired renal function. Spironolactone is contraindicated in patients with acute renal insufficiency or hyperkalemia and is not given in combination with another K^+ -sparing diuretic.
- Gastrointestinal disturbances include diarrhea.
- Androgenic side effects include menstrual irregularities and hirsutism.
- CNS disturbances include lethargy and mental confusion.

Amiloride and Triamterene

They are directly acting agents which enhance Na^+ excretion and reduce K^+ loss by acting on ion channels in the distal tubule and collecting duct as shown in figure.

They block the Na^+ transport through ion-channels in the luminal membrane. Since K^+ secretion is dependent on Na^+ entry, these drugs reduce K^+ excretion.

Therapeutic uses

- The osmotic diuretics are used to *reduce cerebrospinal fluid pressure*.
- They transiently *reduce intraocular fluid pressure*.
- They are used as an adjunct in the prevention or treatment of oliguria and anuria.
- The osmotic diuretics, especially mannitol, are used prophylactically for *acute renal failure* in situations such as cardiovascular operations, treatment with nephrotoxic anticancer agents, severe traumatic injury, and management of hemolytic transfusion reactions.
- Forced diuresis in hypnotic or other substance poisoning.

Adverse effects

- Because they do not penetrate cells and their mode of excretion is by glomerular filtration, osmotic diuretics increase blood volume, which can cause decompensation in patients with congestive heart failure.
- When osmotic diuretics are used for the treatment of renal failure or cirrhotic disease, hyperosmolality and hyponatremia can occur.

Glycerol is effective orally—reduces intraocular and intracranial pressure.

Methylxanthines like theophylline have mild diuretic effect.

Diuretics and Drug Interactions with other drugs

1. Other ototoxic drugs like aminoglycosides should not be used with loop diuretics to avoid enhanced toxicity.
2. NSAIDs blunt the effect of diuretics as they cause salt and water retention.
3. Frusemide and ethacrynic acid are highly protein bound and may compete with drugs like warfarin and clofibrate for protein binding sites.
4. Hypokalemia induced by diuretics enhance digitalis toxicity.
5. Diuretics enhance lithium toxicity by reducing renal excretion of lithium.
6. Other drugs that cause hyperkalemia (ACE inhibitors) and oral K⁺ supplements should be avoided with K⁺ sparing diuretics as together they can cause severe hyperkalemia.

The dose and duration of action of some commonly used diuretic agents are described in Table 6.1.1, while their adverse effects are described in Table 6.1.2.

Table 6.1.1: Dose and duration of action of commonly used diuretics

Diuretic	Daily dose (mg)	Duration (hrs)	Brand name
Furosemide	20-80 mg	3-6	LASIX
Bumetanide	0.5-2 mg	3-6	BUMET
Hydrochlorothiazide	25-100	8-12	ESIDEREX
Polythiazide	1-3	24-48	NEPHRIL
Chlorthalidone	50-100	48-72	HYTHALTON
Xipamide	20-60	24-36	XIPAMID
Metolazone	5-10	18-24	ZAROXYLIN
Seironolactone	50-100	6-12	ALDACTONE
Triamterene (with benzthiazide)	50-100	4-6	DYTIDE
Amiloride (with frusemide)	5-10	20-24	LASIRIDE

Table 6.1.2: Adverse effects of some diuretics

Diuretic	Hyperglycemia	Hyperuricemia	Hypokalemia	Ototoxicity	Calcium Excretion
Thiazide	+	+	+	–	↓
Ethacrynic acid	+	+	+	+	↑
Furosemide	+	+	+	+	↑
Bumetanide	+	+	+	+	↑
Toresemide	+	+	+	+	↑
Mercurials	–	–	–	–	*
Acetazolamide	–	–	+	–	*
Indapamide	+	+	+	–	↓

Antidiuretic Drugs

Antidiuretics are drugs that reduce urine volume.

These include:

1. Antidiuretic hormone (Vasopressin)
2. Thiazide diuretics
3. Miscellaneous:
 - *Chlorpropamide*
 - *Carbamazepine*

Antidiuretic Hormone (ADH)

- Chemically it is an octapeptide.
- It is secreted by the posterior pituitary along with oxytocin.
- It is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, transported along the hypothalamic-hypophyseal tract to the posterior pituitary and it is stored there.
- ADH is released in response to two stimuli: dehydration and rise in plasma osmolarity.
- ADH secretion is stimulated (enhanced) by prostaglandin, angiotensin II, Ach and neuropeptide Y.
- While its secretion is inhibited by: ANP (atrial natriuretic peptide).
- Orally it is inactive (destroyed by trypsin and $t_{1/2} = 25$ min (short)).

Actions

- ADH acts on V_1 and V_2 receptors. V_1 receptors are present in smooth muscles, kidneys and anterior pituitary; V_2 receptors in collecting duct in the kidneys.
- ADH enhances water reabsorption, causes vasoconstriction and raises BP. It also acts on other smooth muscles to increase peristalsis in the gut and contracts the uterus.
- It is given parenterally as injection or as intranasal spray.

Uses

1. Diabetes insipidus of pituitary origin—Desmopressin is the preparation. It should be used life long.

2. Bed wetting in children and nocturia.
3. Bleeding esophageal (Varices) – ADH constricts mesenteric blood vessels and may help in this situation.
4. Before abdominal radiography – expels gases from the bowel.
5. Hemophilia – may release factor VIII and Von-willebrand's factor.

Adverse effects

- When used intranasally ADH can cause nasal irritation, allergy, rhinitis and atrophy of nasal mucosa and sometimes bleeding from nose.
- Other effects include nausea, abdominal cramps and backache in females (due to contraction of the uterus).
- Mammalian ADH is AVP (8-arginine-vasopressin) and can cause bradycardia or precipitate angina. Therefore, it is contraindicated in patients with ischemic heart diseases.

Thiazides

In general thiazide is a diuretic, but paradoxically thiazides reduce urine volume in patients of **diabetes insipidus** of both pituitary and renal origin by an unknown mechanism. Possibly

- Thiazide induces a state of sustained electrolyte depletion so that glomerular filtrate is more completely reabsorbed iso-osmotically in PT. (Proximal tubule)
- Thiazide reduces glomerular filtration rate (GFR) and thus reduces the fluid load on tubules.
 - K^+ supplement are needed with thiazide therapy.
 - Dose : 25–50 mg TDS.

Indomethacin

It can also be used for controlling polyurea to some extent in patients of renal DI. (Diabetes insipidus)

Chlorpropamide

It is an oral hypoglycemic, sensitizes the kidney to ADH action. It is long acting and reduces urine volume in DI [Diabetes Insipidus] of pituitary origin. Thiazide can be combined with it to increase the efficacy.

Carbamazepine

It is an antiepileptic. Its mechanism of action of reducing urine volume is not clear. It stimulates

ADH secretion. Adverse effects are very much therefore it is not used in the treatment of DI. [Diabetes Insipidus]

Clofibrate

Basically, a hypolipidemic drug: It is indicated in neurogenic Diabetes Insipidus. It has unpredictable efficacy and wide range of side effects therefore like carbamazepine it is also not used frequently.



S E C T I O N

7

Cardiovascular System

Hypertension and Antihypertensive Drugs

Blood Pressure: Pressure exerted by the blood on the lateral wall of the larger blood vessels (arteries).

- Systolic blood pressure: 120 ± 10 mm of Hg.
- Diastolic blood pressure: 80 ± 5 mm of Hg.

Maximum normal range of BP **Systolic BP ≤ 139 mm of Hg**, while **Diastolic BP ≤ 89 mm of Hg**.

Factors Regulating Blood Pressure (Fig.7.1.1)

- **BP = Cardiac output $\times$ peripheral resistance**
- **CO = Heart rate $\times$ stroke volume.**
- Stroke volume depends upon (a) end diastolic volume and (b) contractility.
- End diastolic volume depends upon Circulating blood volume.

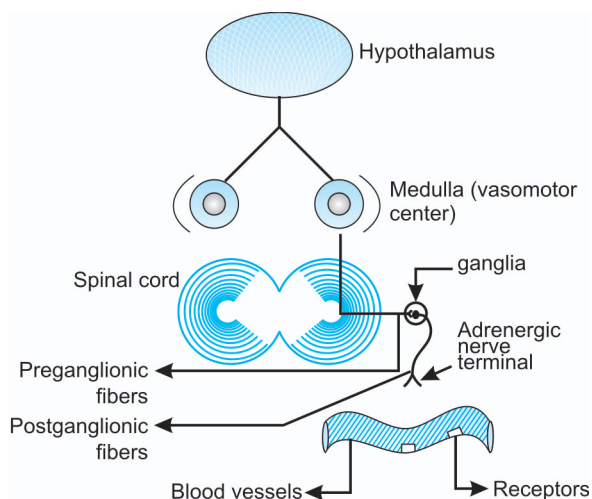


Fig. 7.1.1: Regulation of BP

Hypertension: Hypertension is an elevation of systolic and/or diastolic BP **above 140/90 mm of Hg**. It is a common cardiovascular disorder. Hypertension may be:

1. Primary (essential) hypertension: Where the cause (etiology) is not known about > 90% of hypertension is primary type.

2. Secondary hypertension: When it is secondary to other conditions like; renal, endocrine or vascular disorders.

3. Isolated systolic hypertension: When systolic BP ≥ 160 mm of Hg and diastolic BP ≤ 90 mm of Hg.

Based on the degree of severity, hypertension can be graded as:

- **Mild hypertension: Diastolic BP up to 104 mm Hg.**
- **Moderate hypertension: 105-114 mm Hg.**
- **Severe hypertension: More than 115 mm Hg.**

Normal Homeostasis Mechanism Controlling BP

- Blood pressure is determined by cardiac output (CO) and total peripheral vascular resistance (PVR).
- Blood pressure is controlled by baroreceptor reflexes acting through autonomic nervous system along with the renin-angiotensin-aldosterone system.

A. Short-term regulation of BP (Fig. 7.1.2): Blood pressure controlled by this mechanism involves BP regulation during posture change and emergent conditions.

B. Long term regulation of BP: Renin – Angiotensin: Aldosterone Mechanism (Fig. 7.1.3):

- Stimulus for higher renin secretion
 1. Decrease in hydrostatic pressure in afferent arteriole.
 2. Decrease in Na concentration in Macula densa (Fig. 7.1.4).
 3. Accentuates ANS (sympathetic) stimulation.

Factors (Etiology) for Hypertension

1. Exaggerated adrenergic activity:

- Centrally
- Peripherally

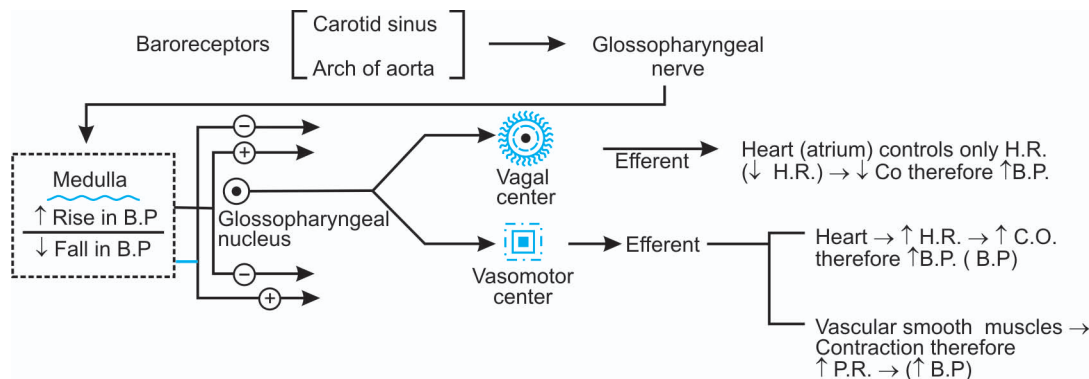


Fig. 7.1.2: Mechanism of short-term regulation of BP

2. High cardiac output due to:

- Rise in heart rate
- Rise in force of contraction
- Rise in blood volume

3. Increased peripheral resistance:

- Due to high vasoconstriction

4. High Na⁺—water retention:

- High renin
- High Angiotensin II
- High Aldosterone activity

5. Most important causes in primary hypertension:

- Increased in plasma renin activity.
- Increase peripheral resistance (arteriolar origin).
- Decrease vascular synthesis of NO.
- Increase in Na⁺ concentration in vascular epithelium.
- Hyper-insulinemia.
- Abnormal synthesis of steroid.

6. Causes of secondary hypertension (all diseases):

- Pheochromocytoma
- Polycystic kidney
- Pylonephritis
- Glomerulonephritis
- Stenosis of renal vessels

Prolonged hypertension damages the blood vessels of the heart, brain and the kidneys and may result in several complications like stroke, coronary artery disease or renal failure. Hence hypertension needs to be treated.

Antihypertensives act by influencing the BP regulatory systems viz the Autonomic system, Cardiovascular system, Renin-angiotensin system, Calcium channels or Sodium and water balance (plasma volume).

• Postural hypotension:

Various drugs produce postural hypotension, as a side effect. It is explained here.

When a person is standing or stands suddenly after a lying or sitting posture, about half to one liter of blood is pooled in the vessels (sp. veins) of lower extremity under the influence of gravity. Due to this occurs fall in cardiac inflow and therefore also cardiac output (↓ CO). This ultimately results in cerebral ischemia and therefore giddiness, but normally this does not occur because of compensatory mechanism, i.e. (Short-term regulation) of Blood Pressure. But if there occurs any disturbance or blockade in this STR, postural hypotension develops.

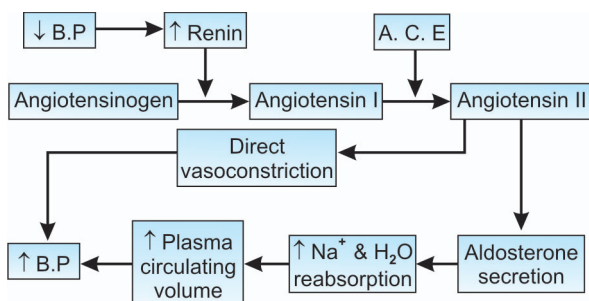


Fig. 7.1.3: Long-term regulation of BP

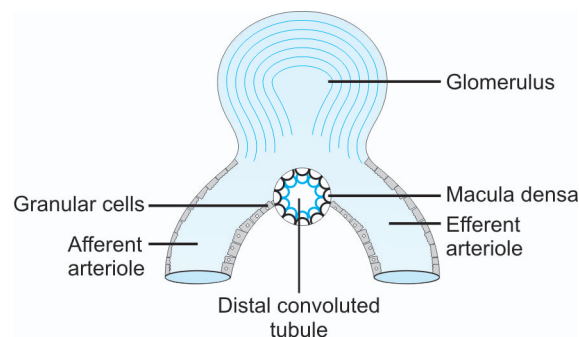


Fig. 7.1.4: Juxtaglomerular apparatus

CLASSIFICATION (FIG. 7.1.5)**1. Diuretics:**

- *Thiazides*: Hydrochlorothiazide, Chlorthalidone, etc.
- *Loop diuretics*: Furosemide (Furosemide)
- *K⁺ sparing diuretics*: Spironolactone, Amiloride, Triamterene.

2. Sympatholytics:

- *Centrally acting drugs*: Clonidine, Methyldopa
- *Ganglion blockers*: Trimethaphan
- *Adrenergic neuron blockers*: Guanethidine, Reserpine.
- *Adrenergic receptor blockers*:
 - β -blockers: Propranolol, Atenolol, etc.
 - α -blockers: Prazosin
 - *Mixed α - and β -blockers*: Labetalol.

3. Vasodilators:

- *Arteriolar dilators*: Hydralazine, Minoxidil, Diazoxide
- *Arteriolar and venular dilators*: Sodium nitropruside

4. Ca⁺⁺ channel blockers: Verapamil, Nifedipine, Diltiazem, Amlodipine, etc.**5. Angiotensin converting enzyme (ACE) inhibitors:**

- Captopril, Enalapril, Lisinopril, Ramipril.

6. Angiotensin II receptor antagonist: Losartan.**7. Miscellaneous:** Pepstatin, Ketanserin, Nicorandil, Veratrum, metyrosin, etc.

Diuretics: Thiazide and loop diuretics, they are the useful drugs when used alone or in combination to reduce hypertension.

- The antihypertensive effect of diuretics is mild, BP falls by 10–15 mm of Hg over 15–30 days.
- Diuretics act as antihypertensives as follows: Diuretics enhance the excretion of sodium and water resulting in negative Na⁺ balance.
 1. $\downarrow$ Plasma volume $\rightarrow \downarrow$ cardiac output $\rightarrow \downarrow$ BP
 2. $\downarrow$ Body sodium $\rightarrow$ relaxation of vascular smooth muscles (due to Na⁺ depletion) $\rightarrow \downarrow$ PVR $\rightarrow \downarrow$ BP
- Restriction of dietary salt intake will reduce the dose of the diuretic needed.
- Thiazides are the first-line, and most frequently used antihypertensives. Their initial antihypertensive effect is due to reduction in blood volume; their long-term effect

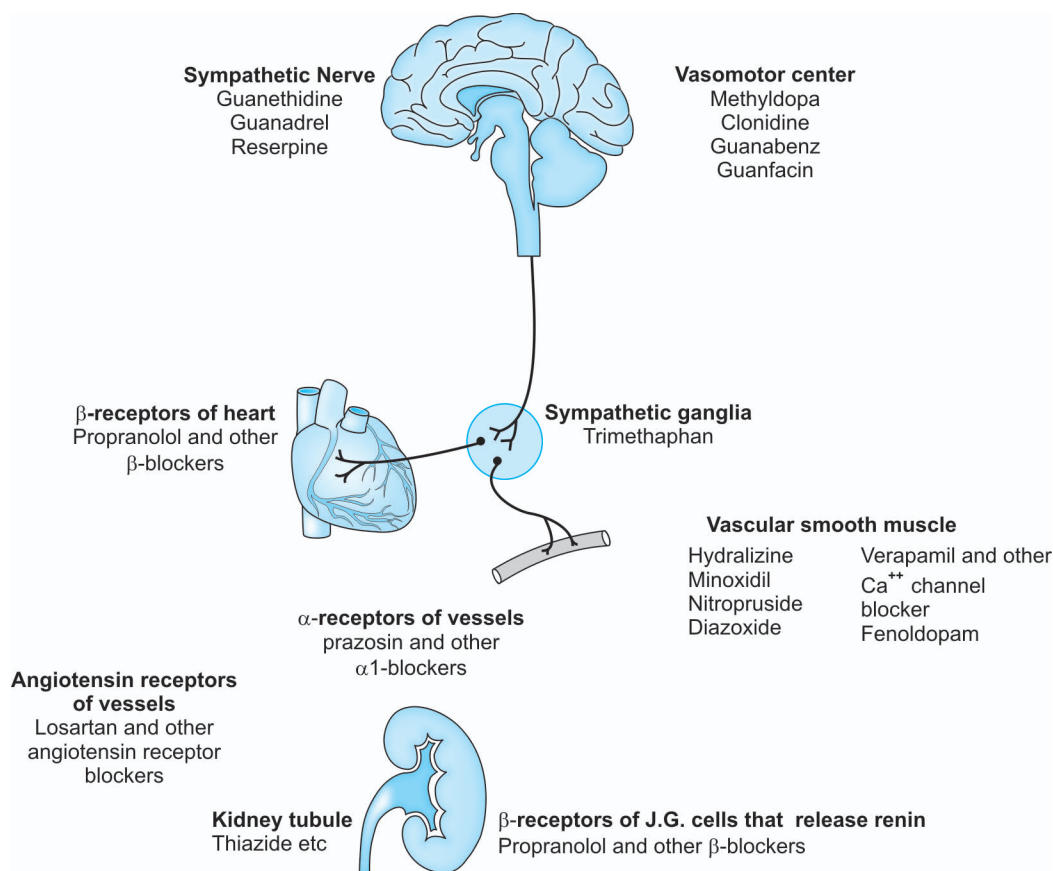


Fig. 7.1.5: Site of action of the major classes of antihypertensive drugs

is related to a reduction in peripheral vascular resistance.

- Thiazides may be used in combination with other antihypertensives. They may be combined with a K⁺ sparing diuretic (like spironolactone) to avoid hypokalemia.
- Loop diuretics produce greater diuresis than the thiazides, but they have a weaker antihypertensive effect and can cause severe electrolyte imbalance. They are used only in hypertension with chronic renal failure or congestive heart failure.
- For details, refer chapter on Diuretic Agents.

SYMPATHOLYTICS

Drugs acting centrally: Clonidine, α -methyldopa, guanabenz and guanfacin act centrally on the vasomotor center of the brain predominantly by stimulating α_2 -adrenergic receptors in the CNS.

The result is decreased sympathetic outflow from CNS.

Clonidine:

- **Clonidine** an imidazoline derivation and is a selective α_2 -agonist.
- Stimulation of α_2 receptors in the CNS (in the vasomotor center and hypothalamus); decreases central sympathetic outflow; blocks the release of noradrenaline from the nerve terminals leading to a fall in BP and bradycardia.
- α_2 -adrenergic agonists lower atrial pressure and also reduces secretion of renin.
- **Clonidine and guanabenz** tend to decrease cardiac output and leave peripheral vascular resistance unchanged.
- Guanfacin has little effect on cardiac output and decreases peripheral vascular resistance.
- **Adverse effects:** include dryness of mouth, nose and eyes, drowsiness; parotid gland swelling and pain, fluid retention, constipation and impotence.
- Sudden withdrawal of clonidine will lead to **rebound hypertension**, headache, tremors, sweating and tachycardia. Hence the dose should be tapered.

Therapeutic uses: Mild hypertension to moderate to severe hypertension.

Clonidine can not be administered to patients taking tricyclic- antidepressants because these drugs block clonidine's hypotensive effect. Clonidine may worsen depression.

Other uses

1. **With anesthetics:** Clonidine given preoperatively reduces the dose of the general anesthetic needed due to its analgesic effects.

2. **In Opioid withdrawal:** Most withdrawal symptoms in opioid addicts are of sympathetic over-activity and can be benefited by treatment with clonidine.

3. **Clonidine controls diarrhea** by improving absorption of NaCl and water in the gut by stimulation of α_2 receptors in the intestines.

α -methyl dopa

- It is an analog of DOPA and is a prodrug.
- Methyldopa is metabolised by decarboxylation and beta hydroxylation in adrenergic neurons of the CNS. The metabolite α -methyl norepinephrine, which is an α_2 agonist, stimulates α_2 receptors like clonidine in the brain, inhibiting sympathetic outflow.
- Methyldopa is poorly absorbed, It will be administered orally or paxenterally by slow i.v., excreted largely by the kidneys.
- It reduces BP and peripheral vascular resistance. It has little effect on CO, renal blood flow and GFR. It does not abolish sympathetic reflexes.
- Left ventricular hypertrophy is reversed in about 12 weeks of treatment.
- **Adverse effects** are sedation, dryness of mouth and nose, headache, postural hypotension, fluid retention and impotence.

Therapeutic uses: It is used in mild to moderate hypertension along with a diuretic.

Ganglion Blockers - Trimethaphan

- Trimethaphan is the only rapid and short acting (15 minutes) ganglion blocker used intravenously to produce controlled hypotension during certain surgeries.
- These drugs block both sympathetic and parasympathetic ganglia resulting in decreased sympathetic tone and a fall in BP.
- They produce several **side effects** as they block both ganglia and therefore not used now.

Adrenergic Neuron Blockers

Guanethidine

- It depletes the stores of noradrenaline in the adrenergic neurons.
- It produces sympathetic blockade before any appreciable decrease in nor epinephrine stores has occurred; with chronic administration it impairs the release of neurotransmitter from peripheral adrenergic neurons.
- It has direct inhibitory effect on skeletal muscle contraction.
- It also increases the sensitivity of tissues to catecholamine.

- It produces **adverse effects** like orthostatic, i.e. postural hypotension, salt and water retention, diarrhea, sexual dysfunction and muscular aching and weakness can occur, therefore it is also not used now a days.
- **Therapeutic use:** In the treatment of moderate to severe hypertension.

Reserpine

- It is an alkaloid obtained from *Rauwolfia serpentina* (Sarpagandha) that grown in India.
- In the neurons, it binds to the vesicles that store monoamines like noradrenaline, dopamine and 5-HT and destroys these vesicles. It thus depletes the stores of these monoamines in the peripheral and central nervous system and cause impaired sympathetic nerve discharge.
- It usually reduces heart rate and cardiac output and may decrease peripheral vascular resistance, therefore ultimately reduces BP.
- **Adverse effects:** It causes episode of severe depression, drowsiness, parkinsonism, postural hypotension, edema and sexual dysfunction. Hence it is generally not preferred.
- It is contraindicated in the patients with active peptic ulcer.
- **Therapeutic use:** It is used in low doses in combination with other anti-hypertensives to control moderate hypertension.

β -blockers

- They are mild to moderate antihypertensives and are useful both alone and in combination with other antihypertensive agents.
- The exact mechanism of action is not known, probably:
 1. They reduce the BP due to a fall in the cardiac output.
 2. They also lower plasma renin activity and an additional central antihypertensive action.
- They are well-tolerated and are of special value in patients who also have history of arrhythmias or angina.
- They are also suitable for combination with other antihypertensives.
- Atenolol is a preferable β -blocker because of advantages like once a day dosing, absence of CNS side effects and β_1 selectivity.
- β -blockers should always be tapered gradually while withdrawing.
- **Adverse effects:** They can exacerbate CHF, asthma, and COPD. They can mask symptoms of hypoglycemia in diabetic patients.

α -blockers

- Prazosin is a quinazoline derivative and is a selective α_1 -blocker; it dilates both arterioles and venules.
- It reduces peripheral vascular resistance and lowers atrial blood pressure in both supine and erect patients with only mild tachycardia.
- Prazosin does not adversely affect insulin sensitivity or blood lipid.
- 'First dose' phenomenon can be avoided by starting with a low dose (0.5 mg) given at bed time. Dose is gradually increased.
- Prazosin is used in mild to moderate hypertension; it may be combined with diuretics and β -blockers.
- **Adverse effects:** Dizziness, palpitation,
- It is also used in the treatment of acute CHF

α - and β -blockers

- Labetalol blocks α_1 and β -receptors.
- Labetalol, is a nonselective β -blocker but possesses intrinsic sympathomimetic activity and blocks vascular postsynaptic alpha adrenergic receptors.
- It is used IV in the treatment of hypertension in pheochromocytoma and in hypertensive emergencies.
- Labetalol on chronic administration may produce orthostatic hypotension and sexual dysfunctions.

Vascular Smooth Muscle

- Vascular smooth muscles are controlled by mediators secreted by sympathetic nerves and vascular endothelium, and by circulating hormones.
- Smooth muscle cell contraction is initiated by a rise in (Ca^{++}) which activates myosin-light-chain kinase, causing phosphorylation of myosin or by sensitization of the my filaments to Ca^{++} by inhibition of myosin-phosphates.
- Agents causing contraction may:
 - Release intracellular Ca^{++} , secondary to receptor-mediated IP_3 formation.
 - Depolarize the membrane and thus allow Ca^{++} entry through voltage-gated Ca^{++} channels.
 - Allow Ca^{++} entry through receptor-operated Ca^{++} channels.
- Agents causing relaxation may:
 - Inhibit Ca^{++} entry through voltage-gated Ca^{++} channels either directly (e.g. Nifedipine) or indirectly by hyperpolarizing the membrane (K^+ activators, e.g. Nicorandil)
 - Increase intracellular cAMP or cGMP concentration; cAMP causes inactivation of myosin-light-chain kinase, and may facilitate increases in $[\text{Ca}^{++}]_i$

The role of the endothelium in controlling vascular smooth muscle

- Endothelial cells release various vasoactive substances, including prostacyclin (vasodilator) and endothelin (vasoconstrictor).
- Many vasodilator substances (e.g. acetylcholine and bradykinin) act via endothelial NO production when $(Ca^{++})_i$ increases in the endothelial cell.
- NO causes smooth muscle relaxation by increasing cGMP formation.
- Endothelin is a potent and long-acting vasoconstrictor peptide, released from endothelial cells by many chemical and exact physical factors. It is confined to blood vessels, and its exact physiological role is not clear.

Vasodilators

- Vasodilators relax the vascular smooth muscles thus reduces BP due to decreased peripheral vascular resistance.
- Salt and water retention and reflex tachycardia are common with vasodilators.

Arteriolar (Direct) Vasodilators

- This group of drugs directly relaxes arteriolar smooth muscles.
- These drugs also increase plasma **renin** activity, causing a **pressor effect**.
- These drugs often cause salt and water retention and thus used in conjugation with diuretic and beta adrenergic blocking therapy.

Hydralazine

- It is a phthalazine derivative, directly acting arteriolar dilator.
- It reduces more diastolic than systolic BP.
- The fall in BP is associated with reflex tachycardia, renin release and fluid retention. Coronary, cerebral and renal blood flow are increased.
- **Adverse effects** are headache, flushing, palpitation, salt and water retention. It may precipitates angina in some patients. Hypersensitivity reactions like serum sickness and lupus erythematosus may occur.
- **Uses:** Hydralazine is used with a β -blocker and /or a diuretic in moderate to severe hypertension not controlled by the first line drugs. It can be given to treat hypertension in pregnancy.
- *It has also been used in the treatment of acute and chronic CHF.*

Minoxidil

- It is a piperidinopyrimidine derivative. It is a directly acting arteriolar dilator used in severe hypertension not responding to other drugs.
- It acts by opening K^+ channels in smooth muscles.
- It reduces peripheral vascular resistance as well as renal vascular resistance while preserving renal blood flow and GFR.
- **Therapeutic Use:** In the treatment of Severe Hypertension specially when it is coupled with renal function impairment.
- Minoxidil stimulates the growth of hair on prolonged use. Hence it is used topically (2% solution) in *alopecia*. Young men with relative alopecia are more likely to respond.

Diazoxide

- It is chemically similar to the thiazide diuretic and is a potent arteriolar dilator.
- It has little action on capacitance vessels.
- Its mechanism of action is like minoxidil.
- It causes fall in both systolic and diastolic blood pressure, accompanied by an increase in both heart rate and cardiac output.
- The drug also relaxes other smooth muscles in addition to vascular muscles.
- It is used in **hypertensive emergencies** where monitoring of infusion is not possible. Diazoxide has a long duration of action (24 hours) and is suitable in such situations.
- Diazoxide is also used orally to treat **hypoglycemia** that is caused by hyperinsulinemia.
- **Adverse effects:** It includes severe hypotension, angina, worsening of MI, edema and hyperglycemia.

Arterial and Venous Vasodilators**Sodium nitroprusside**

- It is a rapidly acting vasodilator and it relaxes both arterial and venous smooth muscles but has little effect on other smooth muscles.
- Both peripheral resistance (PR) and cardiac output (CO) are reduced resulting in lower myocardial oxygen consumption.
- **Nitroprusside** acts through the release of nitric oxide which relaxes the vascular smooth muscles.
- Renal blood flow is maintained with nitroprusside, and **renin** secretion is increased.
- On IV administration, it is rapid (acts within 30 seconds) and short-acting (duration 3 minutes) allowing titration of the dose. This makes it suitable for use in hypertensive emergencies with close monitoring.

- It decomposes on exposure to light; the infusion bottle and tubing should be covered with opaque foil.
- **Adverse reactions:** It includes palpitation, sweating, weakness, nausea, vomiting and in high doses thiocyanate toxicity including psychosis.
- **Therapeutic uses:**
 1. Nitroprusside is the drug of choice in **hypertensive emergencies**.
 2. It can also be used to produce controlled hypotension to **minimize bleeding** during surgery
 3. It can also be used in the treatment of **acute (Congestive heart failure) CHF**.
 4. It is used in situations where short-term reduction of myocardial work load is required as in myocardial infarction, where it can improve **left ventricular function**.

Calcium Channel Blockers (CCBs)

- Calcium channel blockers (CCBs) are another important group of antihypertensives by virtue of their vasodilating effect.
- They dilate the arterioles resulting in reduced peripheral vascular resistance.
- Nifedipine produces some reflex tachycardia, while this is not seen with verapamil, diltiazem and amlodipine as they are cardiac depressants.
- Diltiazem and verapamil depress A-V conduction and should not be used with beta-blockers.
- Fluid retention is negligible unlike other arteriolar dilators.
 - CCBs are well-tolerated, safe and effective.
 - Sublingual nifedipine used in hypertensive emergencies effectively lowers BP in 10 minutes.
 - CCBs are of special value in patients who also have angina.
 - Calcium channel blockers are used for short periods to control hypertension.

- Diuretics may enhance the efficacy of Ca^{++} channel blockers.
- Verapamil can cause severe constipation.

Drugs that interfere with the Renin-Angiotensin System

The kidneys synthesize renin, which act on a plasma globulin substrate to produce angiotensin I. This, in turn, is converted (by Angiotensin Converting Enzyme, a peptidyl dipeptidase) to angiotensin II, a potent vasoconstrictor. Drug in this exert an antihypertensive effect by interfering with either reducing the formation or enhancing the utilization of angiotensin II.

Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors include: Captopril, enalapril, lisinopril, benazepril, fosinopril, quinapril, and ramipril.

- Angiotensin II is a potent direct vasoconstrictor agent, (directly rises BP).
- Angiotensin II also stimulates the secretion of Aldosterone.
- *Aldosterone raises the BP by increasing the plasma volume. (See Fig. 7.1.6)*

Angiotensinogen

↓ Renin

Angiotensin I

↓ ACE

Angiotensin II

↓

Angiotensin III

↓

Aldosterone → Salt and water retention

-----→ Vasoconstriction

↓

↑ BP

↑ Blood volume

Fig. 7.1.6: Renin-angiotensin system

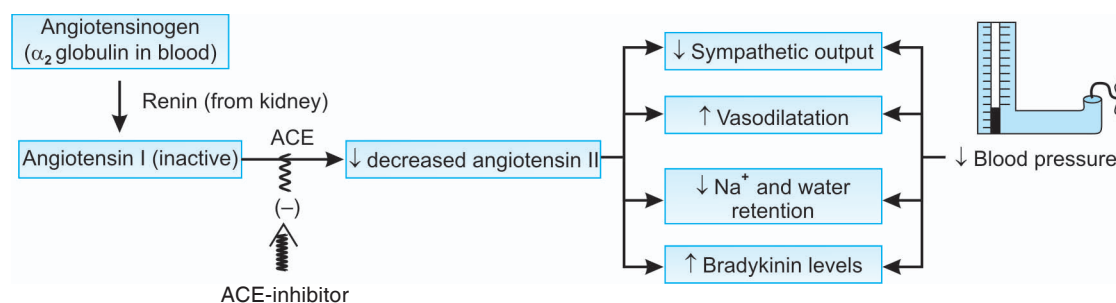


Fig. 7.1.7: Effect of ACE inhibitor

Mechanism of action of ACE inhibitors: ACE inhibitors prevent the formation of angiotensin II and (indirectly) aldosterone as shown in Figure 7.1.7.

- There is vasodilation and decrease in PVR resulting in ↓ BP.
- As ACE also degrades bradykinin, ACE inhibitors raise the bradykinin levels which is a potent vasodilator. This also contributes to the fall in BP.
- The blood flow to the kidneys, brain and heart increases due to selective vasodilatation and thus maintains adequate blood supply to these vital organs.
- **Pharmacokinetics:**
ACE inhibitors are generally well-absorbed. Except *captopril* and *lisinopril* all others are prodrugs.
- **Adverse effects:** ACE inhibitors are well-tolerated. Adverse effects include persistent dry cough (due to -bradykinin levels), hyperkalemia, alteration of taste sensation (dysgeusia), skin rashes, hypotension, headache, nausea, abdominal pain and blood disorders. Angioedema though rare can be severe.
- Dose and duration of action of some commonly used ACE inhibitors are shown in Table 7.1.1.

Table 7.1.1: Dose and duration of action of some commonly used ACE inhibitors

Drugs	Duration of action (hrs)	Daily dose (mg)
Captopril	6-12	12.5-50 mg BD
Enalapril	24	2.5-20 mg OD
Lisinopril	>24	5-40 mg OD
Ramipril	8-48	1.25-10 mg OD

Therapeutic uses

1. **Hypertension:** ACE inhibitors are useful in the treatment of hypertension of all grades and due to all causes. Addition of a diuretic potentiates their efficacy.
2. They are presently the first line antihypertensives. They are specially indicated as antihypertensives in:
 - **Patients with diabetes** as ACE inhibitors slows the development of nephropathy.
 - **Renal diseases:** ACE inhibitors slow the progression.
 - **Left ventricular hypertrophy** is gradually reversed by ACE inhibitors.
3. **Myocardial infarction:** ACE inhibitors started within 24 hours to inhibit cardiac remodeling phenomena, and given for several weeks prevent the development of **CCF** Congestive Cardiac Failure and reduce mortality.

4. ACE inhibitors also relieve chronic **CHF** and afterload.
5. They are also useful in the management of:
 - Diabetic nephropathy
 - Progressive renal insufficiency

Angiotensin II Receptor Antagonists

Saralasin: Blocks both AT₁ and AT₂ receptor

- It can be given only by intravenous infusion
- It is primarily used diagnostically to detect a renal cause of hypertension.

Losartan

- It is an *angiotensin II receptor antagonist*.
- There are two subtypes of angiotensin II receptors — AT₁ and AT₂.
- AT₁ receptors present in vascular and myocardial tissue, brain, kidney and adrenal glands. They are blocked by losartan.
- Losartan relaxes vascular smooth muscles, promotes salt and water excretion and reduces plasma volume.
- The advantage of AT II antagonism over ACE inhibitors is that there is no increase in bradykinin levels and its associated adverse effects like dry cough and angioedema are also less.
- **Adverse effects** include hypotension and hyperkalemia. It is contraindicated in pregnancy and lactation.
- **Therapeutic uses:** Losartan (50 mg OD) is used in the treatment of hypertension in similar situations as ACE inhibitors.

Treatment of hypertension

AIMS for treatment of Hypertension:

- To reduce morbidity and mortality
- To prevent development of complication
- To revert the changes (occurred due to hypertension)
- To reduce the risk factors

Non-pharmacological measures:

- Reduce risk factors, i.e. Reduce obesity and cholesterol, Reduce cigarette smoking, reduce alcohol intake, etc.
- Other measures includes: Exercise, Low salt diet, weight reduction, trans-dental meditation, stress management, yoga, aerobics, naturopathy; all go simultaneously in controlling the blood pressure. These measures also help in reducing the doses of the anti-hypertensive needed.

Selection of drugs (antihypertensives) and therapy depends upon the

- Safety of the drug
- Cost of the drug

- Patients complains
- Other pros and cons (benefits)

Combination of antihypertensives

- Usually, during the management of hypertension we proceed, in step by step manner. When it is not possible to achieve adequate control of BP with a single drug, a combination may be used.
- Antihypertensives may also be combined to overcome the side effects of one another. This also allows use of lower doses of each drug.
- Sympatholytics and vasodilators cause fluid retention which can be overcome by adding a diuretic.
- Vasodilators like nifedipine and hydralazine evoke reflex tachycardia. This can be countered by β -blockers, while propranolol may cause initial rise in PVR (peripheral vascular resistance) which is countered by vasodilators.
- Combination of ACE inhibitors and diuretics is synergistic.

Stepwise management of hypertension will be done according to categories as shown in Table 7.1.2.

Table 7.1.2: Stepwise management of hypertension

Step I	One drug only: Thiazide or beta blocker
Step II	Two drugs: Thiazide (<i>Hydrochlorothiazide</i>) and Sympathoplegic (<i>BB, reserpine, prazosin, clonidine, methyl dopa</i>) or ACE inhibitors.
Step III	Three drugs: Vasodilators or Hydralazine/minoxidil or Ca^{++} channel blockers or ACE inhibitors.
Step IV	Add Guanethidine or an ACE inhibitor to above three drugs.

Step I for Mild Hypertension: Diastolic BP (90–104 mm of Hg)

- *Mild hypertension*: Treatment is started with low doses of a single drug—a thiazide diuretic or a β -blocker. If the patient does not adequately respond in 3–4 weeks, an ACE inhibitor or a calcium channel blocker should be tried. If BP is not controlled by one drug, another should be added (Table 7.1.2).

Step II for Moderate Hypertension: Diastolic BP (105–114 mm of Hg)

- *Moderate hypertension*: A combination of a diuretic with a sympatholytic may be given. If response is inadequate a third drug may be tried.

Step III for Severe Hypertension: Diastolic BP (114–120 mm of Hg)

- *Severe hypertension* may be associated with cardiac or renal disorder. A vasodilator with a diuretic and a β -blocker is useful.

Step IV for very Severe Hypertension: Diastolic BP (>120 mm of Hg)

Hypertensive Crisis

- **Hypertensive emergencies**

When blood pressure is required to reduce (control) within minutes:

- Conditions like hypertensive encephalopathy and acute cardiac failure due to hypertension require immediate reduction of BP. Parenteral drugs are preferred. IV sodium nitroprusside under close monitoring is the drug of choice (in some conditions BP should be lowered gradually to avoid ischemia of vital organs). Diazoxide and sublingual nifedipine are alternatives. As soon as possible switch over to oral drugs.

- **Hypertensive urgency:**

When blood pressure is required to reduce (control) within hours:

Nifedipine	: 10 mg chewed or swallowed
Clonidine	: 100 mcg/oral or IM
Captopril	: 25 mg oral
Hydralazine	: 10–20 mg IM or IV slowly
Furosemide	: (only if there is volume overload)

- *Hypertension in pregnancy:*

- When Systolic BP $\geq$ 135 mm of Hg or
- When Diastolic BP $\geq$ 85 mm of Hg

Hypertension in pregnancy may lead to eclampsia

Hypertension $\rightarrow$ Convulsions $\rightarrow$ Fetal Death

Pre-eclampsia: It is the condition before eclampsia.

The drugs found to be safe in pregnancy are:

- Methyldopa
- Hydralazine
- Beta blocker (cardio selective)
- Prazosin
- Clonidine

Drugs should be avoided in pregnancy:

- ACE inhibitors
- Diuretics
- Reserpine

- Non selective beta blockers
- Na nitroprusside (eclampsia)

Basic four groups of drugs which are used as antihypertensives:

- **Calcium channel blockers:** In elderly/Asthmatics/COPD/Isolated systemic hypertension/hypertension in pregnancy.
- **ACE inhibitors:** In young patients/Diabetics/Angina and CCF patients.
- **Beta blockers:** Tense young patients/Non obese.
- **Diuretics:** Elderly patients/Obese/Patients with isolated systolic hypertension.

Contraindications of these groups of drugs:

- **Calcium channel blockers:** In any cardiac patients (angina, MI, etc).
- **ACE inhibitors:** In Pregnancy/high salt consumer/cough/patient with bilateral renal stenosis.
- **Beta blockers:** LVF, CHF, Elder, Diabetics.
- **Diuretics:** Young patients/Gout/Pregnancy and Diabetics.

Cardiac Glycosides and The Drugs used in The Treatment of Congestive Cardiac Failure

The cardiac muscle is a specialized tissue with unique properties like excitability, contractility and automaticity. The myocardium has two types of cells—the contracting cells and the conducting cells. The contracting cells participate in the pumping action of the heart. Parts of the conducting tissue have the characteristic property of automaticity.

Automaticity is the ability of the cell to generate electrical impulses spontaneously. SA node, AV node and His-Purkinje system comprise the conducting tissue of the heart. Normally, the SA node acts as the pace maker.

Autonomic Control of the Heart

- Sympathetic activity, acting through β_1 -adrenoceptors, increases heart rate, contractility and automaticity, but reduces cardiac efficiency (in relation to oxygen consumption).
- β_1 -adrenoceptors act by increasing cAMP formation, which increases calcium currents.
- Parasympathetic activity, acting through M_2 muscarinic receptors, causes cardiac slowing, decreased force of contraction (atria only) and inhibition of AV conduction.
- M_2 -receptors inhibit cAMP formation, and also open K^+ channels, causing hyperpolarization.

Excitability is the ability of the cell to undergo depolarization in response to a stimulus.

Cardiac action potential (Fig. 7.2.1): When a stimulus reaches the cardiac cell, specific ions move into and out of the cell eliciting an action potential. Such movement of ions across the cardiac cell may be divided into phases:

- **Phase 0:** It is rapid depolarization of the cell membrane during which there is fast entry of sodium ions into the cell through the sodium channels. This is followed by repolarization.
- **Phase 1:** It is a short, initial, rapid, repolarization due to efflux of potassium ions.

- **Phase 2:** It is a prolonged plateau phase due to slow entry of calcium ions into the cell through the calcium channels. Cardiac cell differs from other cells in having this phase of action potential.
- **Phase 3:** It is a second period of rapid repolarization with potassium ions moving out of the cell.
- **Phase 4:** It is the resting phase during which potassium ions return into the cell while sodium and calcium ions move out of it and resting membrane potential is restored. All phases are described in Figure 7.2.2.
 - During phase 1 and 2, the cell does not depolarize in response to another impulse, i.e. it is in **absolute refractory** period. But during phases 3 and 4, the cell is in **relative refractory period** and may depolarize in response to a powerful impulse.
 - The cardiac output is determined by heart rate and stroke volume. The stroke volume in turn depends on the preload, afterload and contractility.
 - **Preload** is the load on the heart due to the volume of blood reaching the left ventricle. It depends on the venous return.
 - **Afterload** is the resistance to the left ventricular ejection volume, i.e. the total peripheral resistance.

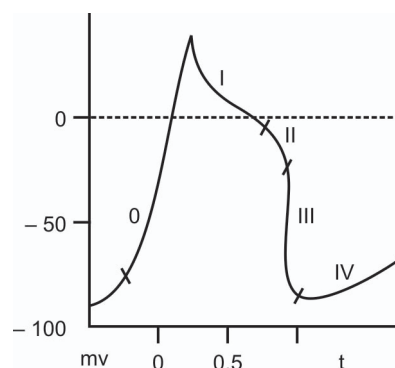
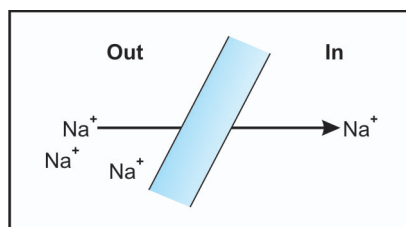
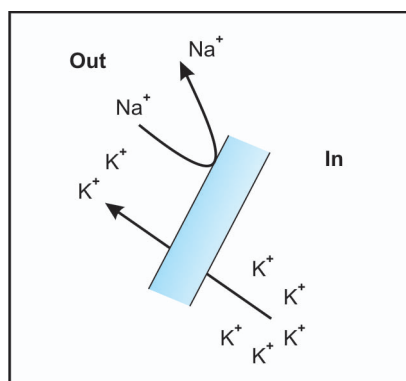
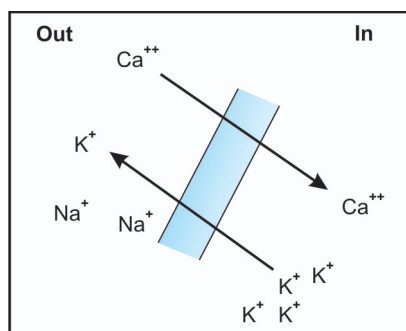
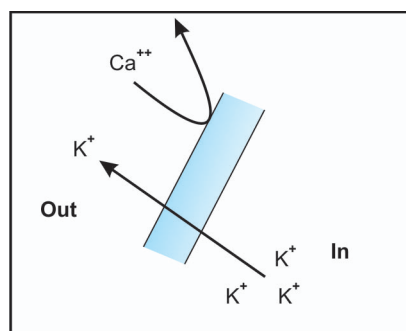


Fig. 7.2.1: Action potential in heart

Phase '0': Fast upstroke**Phase '1': Partial repolarization****Phase 2: Plateau phase****Phase 3: Repolarization****Fig. 7.2.2:** Phases of action potential

Contractility is the ability of the myocardium to adequately contract and pump the blood out of the heart.

Myocardial Contraction

- Controlling factors are:
 - intrinsic contractility
 - extrinsic circulatory factors
- Contractility depends critically on control of intracellular Ca^{2+} , and hence on:
 - Ca^{2+} entry across the cell membrane
 - Ca^{2+} storage in the sarcoplasmic reticulum.
 ⇒ The main factors controlling Ca^{2+} entry are:
 - activity of voltage-gated Ca^{2+} channels
 - $[\text{Na}^+]_i$, which affects $\text{Ca}^{2+}/\text{Na}^+$ exchange.

Many things affect these two processes, including catecholamines and drugs affecting the Na^+ pump.

- Extrinsic control of cardiac contraction is due to the dependence of stroke work on the end-diastolic volume, expressed in the Frank-Starling Law.
- Cardiac work is affected independently by after-load (i.e. peripheral resistance) and pre-load (i.e. central venous pressure).
- 'Heart failure' describes the condition in which the cardiac output is insufficient to meet the circulatory needs of the body (at rest or during exercise).

Congestive Cardiac Failure

Congestive cardiac failure is one of the common causes of morbidity and mortality.

Definition: CHF is defined as the inability of the heart to meet the metabolic requirements of the peripheral systems, i.e.

- The heart is unable to provide adequate blood supply to meet the body's oxygen demand. The pumping ability of the heart is reduced and the cardiac output decreases.

Pathophysiology

- Myocardial cell loss damage resulting from regional ischemia or myopathy leads to deterioration of systolic and diastolic performance.
- When confronted by an increased load, the remaining normal heart hypertrophies to maintain adequate cardiac performance.
 - Hypertrophy results in a fall in stroke volume index and a rise in left ventricular filling pressure.
 - Peripheral vascular resistance increases and pulmonary congestion develops.
- Vasoconstrictor compensatory mechanisms develop to maintain cerebral and coronary perfusion. These include:
 - Stimulation of the sympathetic nervous system

- Stimulation of the renin-angiotensin system
- Release of atrial natriuretic peptide which help in maintaining the cardiac output.

Clinical Manifestations

- These includes pulmonary edema, dyspnea, liver enlargement and peripheral edema.
- The myocardium also undergoes structural alteration like **ventricular hypertrophy** and **remodelling** to adapt itself to the stressful situation. These compensatory changes maintain the cardiac output for some-time.

Factors responsible for CCF

- Low output failure could result from ischemic heart disease, hypertension, valvular and congenital heart diseases.
- High output failure results from anemia, thyrotoxicosis, beriberi and certain congenital heart diseases.

The drugs used in CCF includes diuretics, vasodilators and cardiac glycosides. The pharmacology of **cardiac glycosides** has been discussed first, followed by the role of other drugs in CCF. The cardiovascular consequences of heart failure are shown in Figure 7.2.3.

CARDIAC GLYCOSIDES

History

Cardiac glycosides are obtained from plants of the foxglove family. Though these plants were known to Egyptian 3000 years ago, they were irrationally used. William Withering, an English physician first described the clinical effects of digitalis in CCF in, 1785.

Chemistry

- Cardiac glycosides are the combination of an aglycone, or genin, and one to four sugars.
 1. The aglycone is chemically similar to bile acids and to steroids, such as adrenocortical and sex hormones. It is the pharmacologically active portion of the glycosides.
 2. The sugars modify the water- and lipid-solubility of the glycoside molecule and, thus, affect its potency and duration of action.
- Glycosides are obtained from dried leaves of the foxglove, *Digitalis purpurea* (digitoxin) or *Digitalis lanata* (digitoxin, digoxin), and from the seeds of *strophanthus gratus* (ouabain). The term digitalis is frequently used to refer to the entire group of cardiac glycosides.

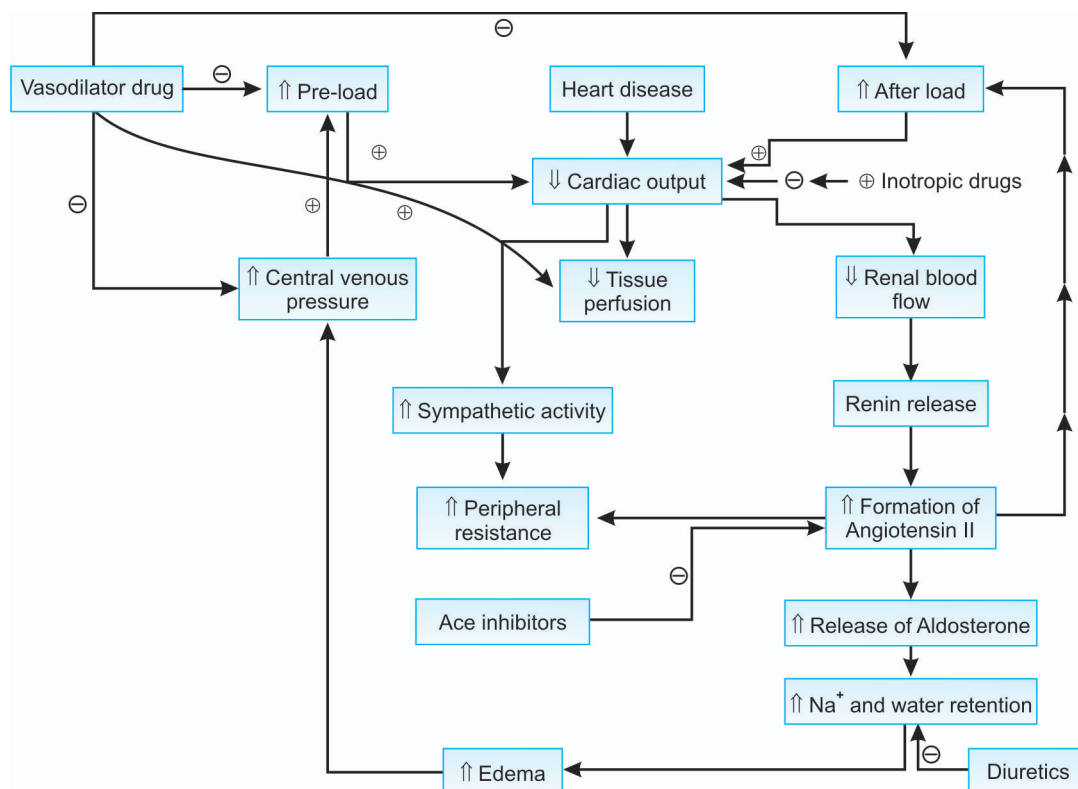


Fig. 7.2.3: Cardiovascular consequences of heart failure

Table 7.2.1: Pharmacokinetics of commonly used cardiac glycoside preparations

	Gastrointestinal absorption	Protein binding	Serum half-life ($t_{1/2}$)	Principal metabolic route	Serum concentration of drugs (ng/ml)	
Digoxin	Approx. 75%	< 30%	36 hours	Kidney	Therapeutic:	0.5-2.5
					Toxic:	>2
Digitoxin	90%-100%	97%	5-7 days	Liver	Therapeutic:	10-35
					Toxic:	>35

Pharmacokinetics**a. Digoxin (Table 7.2.1)**

- The bioavailability varies; intestinal absorption of the drug may be as low as 40%.
- The serum half-life is normally about 36 hours.
- Digoxin is not metabolized and is eliminated principally by the kidneys in almost unchanged form.

b. Digitoxin (Table 7.2.1): Digitoxin is well absorbed (90-100%) from the gastrointestinal tract and does not have the variable bioavailability seen with digoxin.

- The serum half-life of digitoxin is 5-7 days.
- Digitoxin is metabolized by the liver, and drugs that increase the activity of hepatic microsomal enzymes, such as phenobarbital and phenytoin, accelerate its metabolism.
- In contrast to digoxin, digitoxin is approximately 97% bound to plasma albumin.

Pharmacological effects**General considerations**

1. The most important property of cardiac glycosides is their positive inotropic effect, that is, their ability to

increase the force of myocardial contraction. The result is increased cardiac work at reduced metabolic cost.

2. Glycosides also have effects on the electrophysiological properties of the heart (conductivity, refractory period, automaticity).
3. In addition, glycosides have extracardiac effects on vascular smooth muscle, neural tissue, and other tissues.

Effects of cardiac glycosides on the heart

Myocardial contractility: Cardiac glycosides increases the contractility of cardiac muscle by increasing both the velocity of muscle contraction and the maximum force that is developed. Cardiac glycosides appear to exert their positive inotropic effect by following mechanism:

- Digitalis inhibits membrane-bound Na^+ , K^+ -activated adenosine triphosphatase (Na^+ , K^+ -ATPase) thus increasing intracellular Ca^{2+} levels (Fig. 7.2.4).
- In CHF patients, glycosides increase cardiac output, decrease cardiac filling pressures, decrease heart size, and decrease venous and capillary pressures, which is reflected by a downward shift in the ventricular curve.

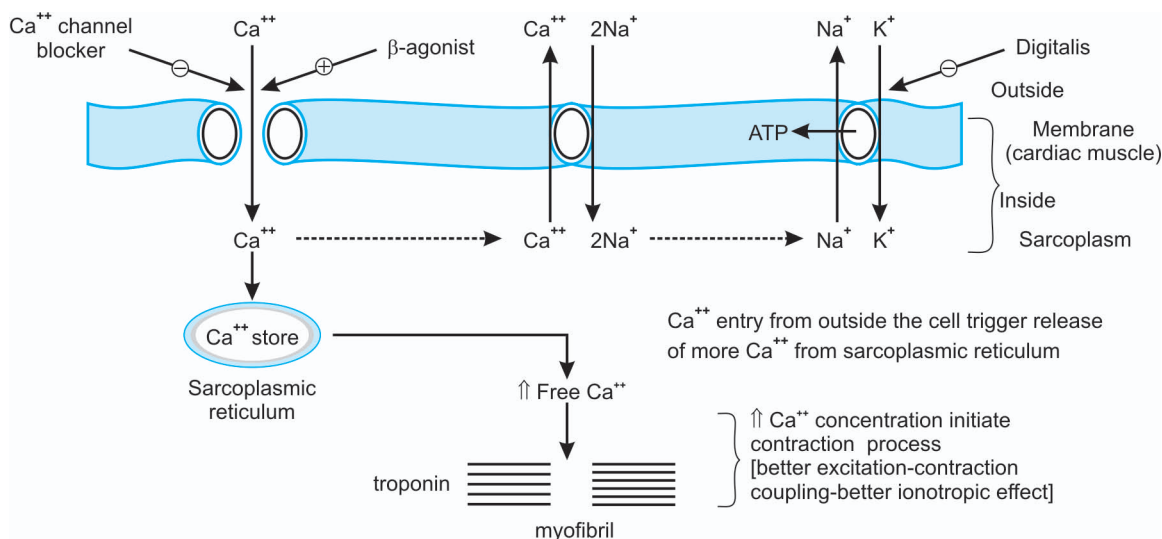


Fig. 7.2.4: Mechanism of action of digitalis

Myocardial oxygen consumption

- The digitalis-induced increase in myocardial contractility causes an **increase in myocardial oxygen consumption**.
- Decreased ventricular volume, resulting from the digitalis-induced increase in muscle tone and cardiac output, **decreases the myocardial oxygen consumption**.

Electrophysiological activity: Cardiac glycosides indirectly increase the vagal tone of the heart. They prolong the refractory period of the atrioventricular (A-V) node and decrease conduction velocity (both directly and indirectly) through the A-V node.

Heart rate: In normal individuals, digitalis has little effect on the heart rate.

- In CHF patients, digitalis **slows the heart rate** (a negative chronotropic effect). This results from vagal nerve stimulation, which slows pacemaker activity at the sinoatrial (S-A) node.
- Excessive doses of digitalis can produce **tachycardia**.

Extracardiac effects

- When cardiac glycosides increase the cardiac output in **CHF patients, there is a drop in peripheral vascular resistance and venomotor tone as well as an increase in blood flow**. In normal individuals, digitalis produces venous and arterial constriction.
- A **diuretic effect** occurs because the increased cardiac output and renal blood flow combine to reduce the neurohumoral factors that inhibit the excretion of salt and water.
- CNS—High doses stimulate CTZ resulting in nausea and vomiting.

Therapeutic uses

- Cardiac glycosides are of greatest value for treating **low-output cardiac failure**.
- They are also of great value in the control of atrial fibrillation and flutter.
- Paroxysmal atrial-tachycardia frequently responds to digitalis therapy, presumably as a result of reflex vagal stimulation.

Contraindications: The use of cardiac glycosides is contraindicated in cardiac tamponade, high-output CHF, constrictive pericarditis, idiopathic hypertrophic subaortic stenosis with outlet obstruction, patients of MI, Hypokalemia, thyrotoxicosis and myxedema.

Digitalization and Maintenance Dosage**Digoxin**

- When there is no urgency, an oral digitalizing dose is first administered, and then the maintenance dose is adjusted on the basis of clinical and laboratory assessment. Usually, a steady-state level is achieved in 5 half-lives (about 8 days).
- When digitalization must be achieved rapidly, digoxin can be administered intravenously over a period of several minutes. The onset of action is within 5-30 minutes; the maximal effect is reached within 1-5 hours.

Digitoxin

- The total oral loading (digitalizing) dose of digitoxin is divided into doses given every 6 hours and administered over the course of 36-48 hours.
- The maximal effect of a dose of digitoxin is reached approximately 9 hours after oral administration.
- Once optimal benefit has been achieved, the maintenance dose usually is adjusted to 10% of the digitalizing dose.

Adverse effects: Digitalis glycosides have a low margin of safety, and intoxication from an excess of the drug is a common and potentially fatal problem [**Digitalis Toxicity**]

- Intoxication is most frequently precipitated by the depletion of serum K^+ caused by diuretic therapy, but it can also occur from accumulation of maintenance glycoside doses taken over a long period of time. Intoxication from hypokalemia may also occur as a result of prolonged administration of corticosteroids, protracted vomiting, and protracted diarrhea.
- When the concentrations of digoxin and digitoxin rise above 2 ng/ml and 35 ng/ml of blood, respectively, signs of systemic toxicity often appear, and therapy must be discontinued. Signs of toxicity include:
 - Anorexia (often the earliest sign)
 - Nausea, vomiting, and diarrhea
 - Headache, fatigue, malaise, neuralgias, and delirium
 - Vision changes, including abnormal color perception
 - Gynecomastia (rare)
 - Cardiac effects:
 - Premature ventricular contractions (PVCs) and ventricular tachycardia and fibrillation
 - A-V dissociation and block
 - Sinus arrhythmia and S-A block

Treatment of digitalis toxicity

- Cardiac glycosides and K^+ -depleting diuretics are discontinued.
- KCl is administered orally or by slow, careful intravenous infusion if hypokalemia is present; K^+ is not given, however, if there is severe A-V block or if serum K^+ levels are high.
- Because hypomagnesemia may accompany hypokalemia, magnesium replacement may also be necessary.
- Phenytoin can be given for ventricular and atrial arrhythmias.
- Lidocaine and procainamide can be used to treat ventricular tachyarrhythmias.
- Propranolol can be used for ventricular and supraventricular tachycardia but not in the presence of A-V block.
- Atropin can be used to control sinus bradycardia and various degrees of A-V block.
 - Cholestyramine binds to cardiac glycosides and has been used to hasten their elimination.
 - A digoxin-specific antibody fragment from immunized sheep is available for the treatment of life-threatening digoxin or digitoxin overdose. Its use is reserved for patients exhibiting shock or cardiac arrest, ventricular arrhythmias, progressive bradyarrhythmias, or severe hyperkalemia.

Other Positive-Inotropic Drugs**Phosphodiesterase Inhibitors****Bipyridine derivative; Amrinone, milrinone:**

- These drugs inhibit the enzyme phosphodiesterase type III (which degrades cAMP) resulting in $\uparrow$ cAMP levels.
- They increase force of contraction and also cause vasodilation.
- Route of administration. This agent is administered intravenously. (IV)
- Adverse effects
 1. A dose-related thrombocytopenia may occur.
 2. Amrinone may increase the ventricular rate in patients with atrial flutter or fibrillation.
- Because of the adverse effects and increased mortality seen with the use of these drugs, they are not preferred. They are reserved for the short-term therapy of CHF that is refractory to other agents.

OTHER DRUGS USED IN CONGESTIVE CARDIAC FAILURE

In congestive cardiac failure (CCF), the heart is unable to provide adequate blood supply to meet the demand. The

aim of treatment is to reduce morbidity and mortality by restoring cardiac output and relieving congestion.

Drugs commonly used in chronic heart failure

- Loop diuretics (e.g. furosemide)
- ACE inhibitors (e.g. captopril, enalapril)
- Digoxin especially for heart failure associated with established rapid atrial fibrillation. It is also indicated in patients who remain symptomatic despite treatment with loop diuretics and ACE inhibitors.
- Other vasodilators: organic nitrates (e.g. isosorbide mononitrate) reduce pre-load, and hydralazine reduces after-load used in combination, these prolong life, but less effectively than ACE inhibitors. They are used when ACE inhibitors are contraindicated or not tolerated.

1. Diuretic therapy and Na^+ restriction: It plays an important role in reducing extracellular fluid volume. Diuretics relieve symptoms of heart failure more rapidly than any other oral agent and, along with digoxin, are first-line drugs in the treatment of CHF.

2. α -adrenergic blocking agents:

They may be used in CHF to improve cardiac function by inducing vasodilation through both direct and reflex actions.

3. Angiotensin-converting enzyme (ACE) inhibitors**Pharmacological effects (Fig. 7.2.5)**

- a. ACE inhibitors (e.g., captopril, enalapril, lisinopril) produce beneficial hemodynamic effects by decreasing the conversion of angiotensin I to angiotensin II. They also inhibit the degradation of bradykinin.
- b. Hemodynamically, these agents increase cardiac output by reducing afterload and by decreasing total peripheral resistance, pulmonary resistance, and preload.
 - *Reduction of afterload* Angiotensin II is a powerful vasoconstrictor present in the plasma in high concentrations in cardiac failure. ACE inhibitors reduce Angiotensin II.
 - *Reduction of preload* Aldosterone causes salt and water retention and increases plasma volume. ACE inhibitors reduce it.
 - *Reversing compensatory changes* Angiotensin II formed locally in the myocardium is responsible for various undesirable compensatory changes like ventricular hypertrophy and ventricular remodeling seen in CCF. ACE inhibitors reverse these changes. ACE inhibitors are the most preferred drugs in chronic congestive cardiac failure.

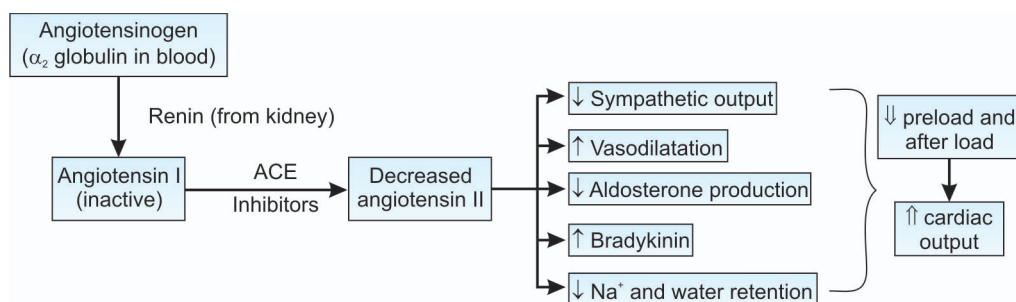


Fig. 7.2.5: Effect of ACE inhibitor

Therapeutic uses

1. Today, ACE inhibitors are used as first-line agents for CHF therapy.
2. Adding an ACE inhibitor to therapy with diuretics and digitalis has increased the survival rate among patients with mild to severe CHF.
3. After myocardial infarction, ACE inhibitors may lessen the progressive enlargement of the left ventricle. (Inhibit remodelling)

Adverse effects

- Severe persistent **cough** occasionally occurs.
- **Hypotension** and **deterioration of renal function** can occur with an ACE inhibitor-diuretic combination.
- **Hypokalemia** and **ventricular arrhythmias** occur in CHF patients given an ACE inhibitor combined with a diuretic.
- Adverse effects associated with captopril, such as **rash, taste disturbances, proteinuria, and leukopenia**, may be related to the sulfhydryl moiety of captopril.

4. Other vasodilators may be used for patients not responding to digitalis glycosides and diuretics.

a. Arteriolar dilators decrease after load, whereas venous vasodilators reduce preload. The decrease in preload and after load increases cardiac output while reducing pulmonary congestion.

b. Isosorbide dinitrate, hydralazine, and prazosin have all been used in the treatment of CHF. Isosorbide improves cardiac function, but it has not been shown to improve survival rates when used alone. Increased survival rates have been demonstrated with isosorbide and hydralazine used together.

5. β-blockers (Metoprolol and bisoprolol)

The immediate hemodynamic action of β-blockers is to depress cardiac contractility and on this presumption, it was not used in the past for the treatment of CHF or even it was contraindicated. But extensive studies over past 20 years have now established that, these parameters (Cardiac depression in contractility due to β-blockers) gradually improves over a week and after few month ejection fraction is generally higher than baseline.

They are now contraindicated only in patients with marked fluid retention.

Drugs Used in the Treatment of Angina Pectoris and Ischemia

ANGINA

Definition: Angina pectoris is the clinical manifestation of ischemic heart disease (IHD) characterized by sudden, severe, sub-sternal discomfort or pain which may radiate to the left shoulder and along the ulnar border of the left arm.

Autonomic innervations is less important.

- The heart has a smaller blood supply in relation to its oxygen consumption compared to most organs.
- Coronary flow controlled mainly by :
 - Physical factors, including transmural pressure during systole.
 - Vasodilator metabolites.

Coronary blood flow depends upon:

- Dilatation of coronary blood vessels
- Hydrostatic pressure.
- Sub-endocardial crunch.
- In Rt. ventricle wall and other tissues: Blood flow during both systole and diastole.
- In Lt. ventricle wall: Blood flow only during diastole.

Normal coronary blood flow can increase upto 500%.

Special features of coronary artery

- Functional end arteries.
- Coronary blood is 30% saturated with oxygen, while blood in skeletal muscle arteries is 60 to 70% saturated with oxygen.

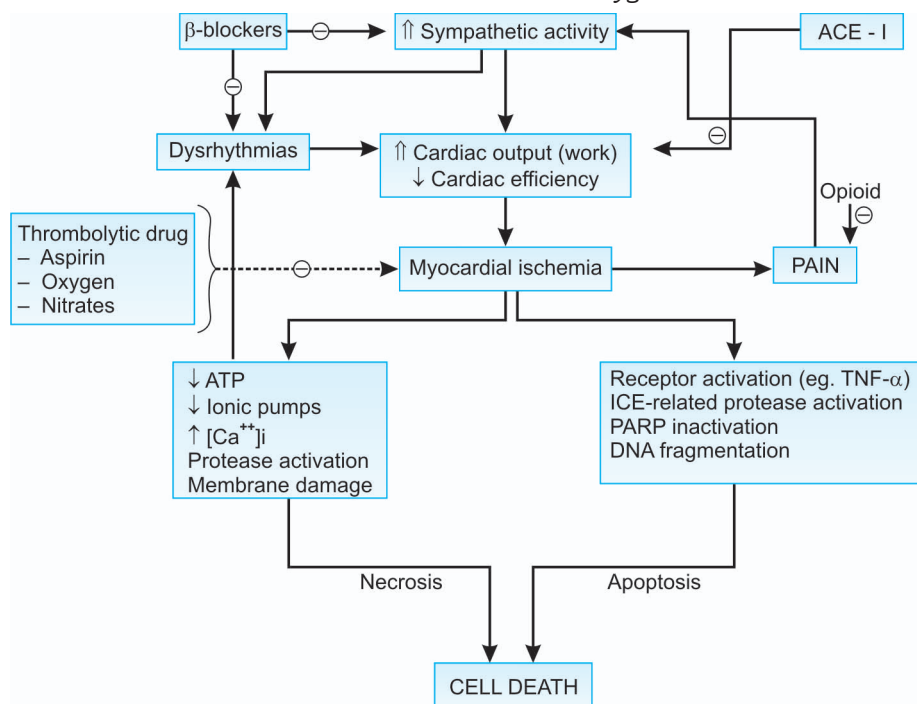


Fig. 7.3.1: Effect of myocardial ischemia

- Therefore, during high demand (exercise), coronary blood oxygen requirement is met only by increase in **coronary blood flow**. While in skeletal muscles, oxygen requirement is met by taking debt from store, i.e. (60 – 70% saturated blood).
- Coronary ischemia is usually due to **atherosclerosis**, and causes **anginal pain**. Sudden ischemia is usually due to **thrombosis**, and may cause **cardiac infarction**.
- Coronary spasm sometimes causes angina (**variant angina**).
- Cellular calcium overload results from ischemia, and may be responsible for:
 - cell death
 - initiation of dysrhythmias/arrhythmias.
- Myocardial oxygen consumption is mainly determined by **preload** (venous return and stretching of the heart), **afterload** (peripheral arterial resistance) and **heart rate**.
- When the oxygen supply to the myocardium is insufficient for its needs (imbalance between oxygen supply and oxygen need); myocardial ischemia develops (Fig. 7.3.1).
- Pain is due to accumulation of metabolites in the cardiac muscle. Three forms of angina are there:
 - 1. Classical angina** (stable angina, angina of effort) pain is induced by exercise or emotion, both of which increase myocardial oxygen demand. As there is narrowing of the coronary arteries due to atherosclerosis, they cannot dilate to increase the blood supply during exercise. Hence there is imbalance between oxygen supply and demand.
 - 2. Variant or Prinzmetal's angina** occurs at rest and is caused by spasm of the coronary artery.

3. Unstable angina: Also occurring at rest, but pain is unstable in frequency and duration. It may deterioratingly progresses to MI.

Drugs are used to improve the balance between oxygen supply and demand either by increasing oxygen supply to the myocardium (coronary dilation) or by reducing the oxygen demand (reducing preload/afterload/heart rate or all of these).

ANTIANGINAL DRUGS

Antianginal drugs are classified in Table 7.3.1.

Table 7.3.1: Classification of antianginal drugs

- 1. Nitrates:** Nitroglycerine, Isosorbide dinitrate, Isosorbide mononitrate, Penta erythritol tetranitrate.
- 2. Calcium channel blockers:** Verapamil, Diltiazem, Amlodipine.
- 3. β -blockers:** Propranolol, Atenolol, etc.
- 4. Potassium channel openers:** Nicorandil, pinacidil etc.
- 5. Antiplatelet drugs:** Aspirin, Dipyridamole
- 6. Miscellaneous:** Trimetazidine (cytoprotective).

NITRATES

Chemistry

- The term nitrates is used in this chapter to encompass both **nitrites** (esters of nitrous acid) and **nitrates** (polyol esters of nitric acid).
- Glyceryl trinitrate (**nitroglycerin**) is the **prototype** of this group.
- Nitroglycerin and amyl nitrite are volatile liquids at room temperature. Other nitrates are solids.

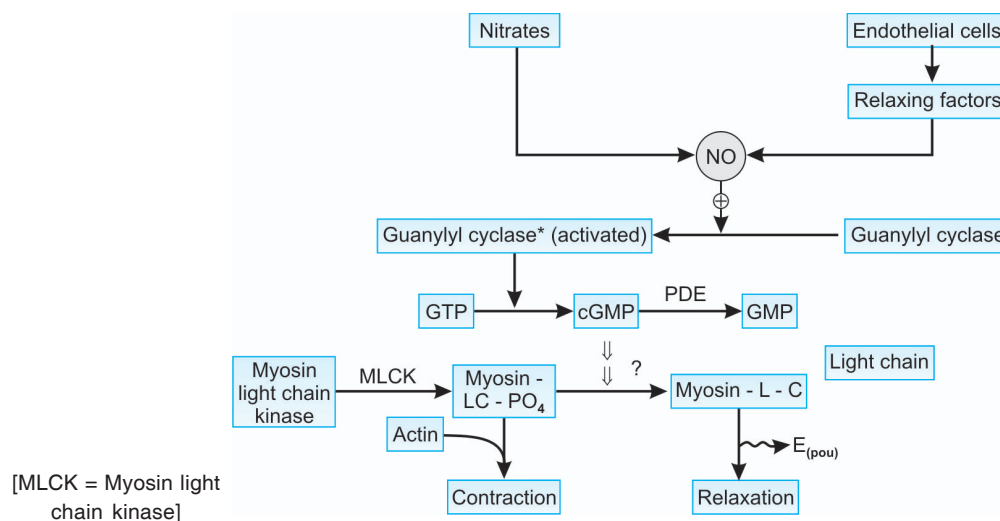


Fig. 7.3.2: Mechanism of action of Nitrates and Nitrites

Mechanism of action (Fig. 7.3.2)

- The nitrates relax all smooth muscle, including vascular smooth muscle. The proposed biochemical action involves the formation of free radical nitric oxide (NO), which stimulates guanylate cyclase. The resultant guanosine 3', 5'-monophosphate (cyclic GMP) activates a protein kinase, which mediates dephosphorylation of myosin. (Figure 7.3.2)
- Nitrates reduce venous tone, thereby increasing venous capacitance and **decreasing venous return** to the heart.
- Nitrates **decrease peripheral arteriolar resistance**.

Pharmacokinetics

- The nitrates are readily absorbed through the buccal mucous membranes, the skin, the gastrointestinal tract, and the lungs.
- The nitrates are broken down in the liver by a glutathione-dependent organic nitrate reductase and are excreted as various nitrites and nitrates.

Pharmacological effects

- Effects on the heart**
 - The major effect of the nitrates on the heart is to reduce myocardial oxygen requirements relative to myocardial oxygen delivery.
 - Nitrates are believed to dilate the large epicardial and collateral coronary arteries selectively, an action that favors the distribution of blood to ischemic areas. (They do not increase the total coronary blood flow in patients with atherosclerosis).
- Extracardiac effects**
 - Vasodilation of cerebral vessels produced by nitrates results in increased intracerebral pressure and sometimes **headache**.
 - The nitrates dilate vessels in the skin, resulting in **flushing**.

Route of administration

- Nitroglycerin is usually given **sublingually**. However, for long-lasting effects, nitroglycerin may be adminis-

tered either **orally or topically** (transdermally) via ointment or patch.

- Nitroglycerin may also be given **intravenously** in medical emergencies.

Some preparations are discussed in Table 7.3.2.

Therapeutic uses

- Stable angina:** Sublingual nitroglycerine is the drug of choice for acute anginal attacks. It relieves pain in 5 minutes. If the pain is not relieved, the dose may be repeated (up to 3 tablets in 15 minutes).
 - Unstable angina:** intravenous glyceryl trinitrate (as supplement to aspirin).
 - Cardiac failure:** Nitrates are useful due to their vasodilator property.
 - Myocardial infarction:** IV nitroglycerine is used by many physicians.
 - Cyanide poisoning:** Nitrates convert hemoglobin to methemoglobin which binds to cyanide, forming cyanmethemoglobin. It thus protects the important enzymes from binding to cyanide. Amyl nitrite is preferred. Early treatment is very important.
- Uses related to relaxation of other smooth muscles (e.g. uterine, biliary) are being investigated.

Adverse effects

- Headache is a common early side effect of nitrates that usually decreases after the first few days of treatment (i.e., patients usually develop tolerance to headache).
- Dizziness, weakness, and cerebral ischemia associated with postural hypotension occasionally occur.
- Nitrite ions, when present in large amounts, can oxidize enough hemoglobin to met-hemoglobin to result in hypoxia.
- Death can occur with acute nitrate poisoning from circulatory collapse or respiratory failure.

Tolerance: When nitrates are appropriately administered intermittently, tolerance does not occur.

Table 7.3.2: Some nitrates used in angina pectoris and myocardial ischemia

Drugs	Dose and route	Duration of action
Nitroglycerine (GTN) (ANGISED)	0.5 mg SL or 5 mg oral or 2% Skin ointment	15-40 mins 4-8 hr 4-6 hrs.
Isosorbide dinitrate (SORBITRATE)	1- 2 inches on the pericardial region 5-10 mg SL or 10-20 mg oral	20-40 min 2-3 hr
Isosorbide mononitrate (ISMO)	10-20 mg oral	6-8 hr

CALCIUM CHANNEL BLOCKERS

- The depolarization of cardiac and vascular smooth muscle cells depend on the entry of extracellular calcium into the cell through calcium channels. This calcium, triggers the release of intracellular calcium from the sarcoplasmic reticulum. All these calcium ions cause contraction.
- Calcium channel blockers (CCB) inhibit the entry of Ca^{++} by blocking the Ca^{++} channels. This results in the following actions:
 - 1. Smooth muscle relaxation:** Arteriolar dilatation reducing peripheral vascular resistance, leading to a fall in BP. Reflex tachycardia may occur with some.
 - 2. Heart:** CCBs depress myocardial contractility, reduce heart rate, cardiac work and myocardial O_2 consumption.
 - 3. Coronary circulation:** Coronary vasodilatation occurs, increasing coronary blood flow. Hence they are useful in variant angina. (Vasospastic type)

Calcium antagonists (CCB)

- Block Ca^{++} entry by preventing opening of voltage-gated L-type and, recently, T-type Ca^{++} channels.
- Three main L-type antagonists, typified by verapamil, diltiazem and dihydropyridines (e.g. nifedipine).

Classification

- Nifedipine, nicardipine, and amlodipine are dihydropyridines. (others are flalodipine, lacidipine, nimodipine, etc.)
- Verapamil
- Diltiazem

Pharmacokinetics

- Verapamil, diltiazem, nifedipine, and nicardipine are rapidly and almost fully absorbed after oral administration. Amlodipine is slowly absorbed.
- Peak blood levels
 1. Nifedipine : 30 minutes
 2. Diltiazem : 1 hour
 3. Verapamil : 1-2 hours
 4. Nicardipine : 8-9 hours
 5. Amlodipine : 6-12 hours
- All five drugs are highly bound by serum proteins.
- Verapamil undergoes extensive first-pass biotransformation in the liver. All five drugs are excreted as metabolites in the urine.

Pharmacological effects (Fig. 7.3.3)

- 1. Cardiovascular effects:** By their inhibition of Ca^{++} influx into myocardial and vascular smooth muscle cells,

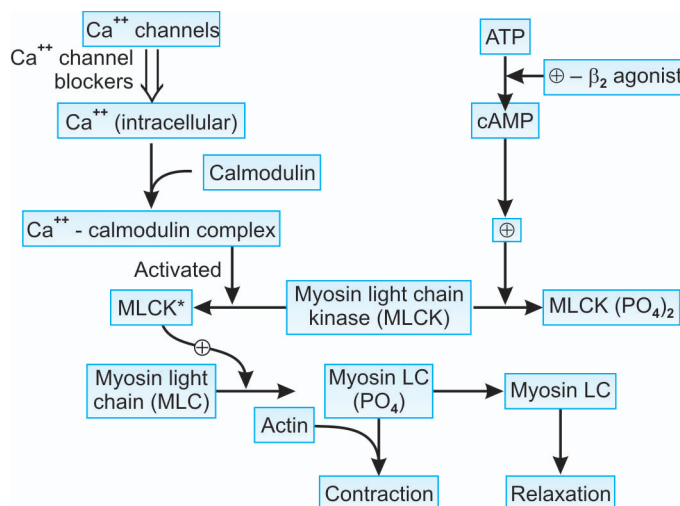


Fig. 7.3.3: Mechanism of action of Ca^{++} channel blockers

Ca^{++} -channel blockers have diverse effects on the cardiovascular system, i.e. $\downarrow \text{FC}$ & $\downarrow \text{H.R.}$

- 2. Extracardiac effects:** Verapamil produces nonspecific sympathetic antagonism and has a local anesthetic effect.

Route of administration: Ca^{++} -channel blockers may be given orally; for use in medical emergencies, verapamil is also available in intravenous form.

Therapeutic uses

- 1. Angina pectoris:** Ca^{++} -channel blockers are useful in the treatment of both Prinzmetal's angina and classic exertional angina. Nifedipine appears to be the most effective for Prinzmetal's angina.
- 2. Nifedipine:** It can be combined with β -blockers like propranolol. Nifedipine can be used in premature labor.
- 3. Hypertension:** Verapamil, nifedipine, amlodipine and diltiazem can be used. Nifedipine is used sublingually in hypertensive crisis.
- 4. Arrhythmias:** Verapamil is the drug of choice in PSVT.
- 5. Migraine:** The Ca^{++} channel blockers are being studied for their value in migraine treatment.
- 6. Peripheral vascular disease:** Nifedipine is useful in Raynaud's disease due to its vasodilator effects. Verapamil can be used in night leg cramps.

Adverse effects

- The Ca^{++} -channel blockers, perhaps especially when used in combination with β -adrenergic blocking agents, can produce or aggravate the following:
 - Hypotension and Bradycardia.
 - A-V block
 - CHF
 - Asystole

- Most of the adverse effects are mild; dizziness and peripheral edema are among the more common adverse effects. Others include nausea and constipation.

Unlike other dehydropyridines, amlodipine does not cause reflex tachycardia

β-BLOCKERS

- β-blockers reduce the frequency and severity of attacks of exertional angina and are useful in the prevention of angina.
- Exercise, emotion and similar situations increase sympathetic activity leading to increased heart-rate, force of contraction and BP, thereby increasing O₂ consumption by the heart.

Propranolol

Mechanism of action

- β-blockers prevent angina by blocking all these actions due to sympathetic overactivity. They are used for the long-term prophylaxis of **classical angina** and may be combined with nitrates.
- Propranolol may also decrease arterial pressure.

Route of administration: Propranolol is usually administered orally for the treatment of angina.

Therapeutic uses

- Propranolol is used prophylactically to decrease the severity and frequency of anginal attacks.
- Propranolol can be administered concomitantly with nitroglycerin, in that case it reduces the amount of nitroglycerin needed to control angina.
- Propranolol should not be used for Prinzmetal's (variant) angina, which is caused by coronary vasospasm.

Adverse effects

- Propranolol can worsen CHF and can **precipitate bronchospasm** in patients with bronchial asthma
- Bradycardia and hypotension can occur.
- Renal plasma flow and glomerular filtration rate may be reduced.

β-blockers should always be tapered after prolonged use. They are not useful in variant angina.

[POTASSIUM CHANNEL OPENERS]

Nicorandil

- It is an arteriovenous dilator.
- Opening of the K⁺ channels results in hyperpolarization and therefore relaxation of the vascular smooth muscles.
- **Adverse effects:** These are headache, flushing, dizziness and hypotension, etc.
- **Uses:** Angina and MI.

[Dipyridamole]

- It is a coronary vasodilator but it diverts the blood from ischemic zone and is therefore not beneficial.
- It inhibits platelet aggregation for which it is used in post—MI and post-stroke patients for prevention of coronary and cerebral thrombosis.

Trimetazidine

- Mechanism of action is unknown by non hemodynamics. It ↓ frequency of angina & ↑ exercise tolerance in patients.

[PHARMACOTHERAPY OF ANGINA]

- In acute attack sublingual nitroglycerine is the drug of choice. If the pain does not subside in 5 minutes, repeat the dose (maximum up to three tablets). After the relief of pain, the tablet should be discarded.
- For acute prophylaxis sublingual nitroglycerine should be given 15 minutes before an exertion (e.g. walking uphill) can prevent the attack. The prophylactic effect lasts for 30 minutes.
- In chronic prophylaxis long-acting nitrates or β-blockers (preferred) or calcium channel blockers can be used. All are given orally.

If one drug is not effective, a combination of drugs may be used.

[COMBINATIONS OF DRUGS IN ANGINA]

1. Nitrates + β-blockers—very effective in exertional angina.
Reflex tachycardia due to nitrates is countered by β-blockers. Ventricular dilatation due to β-blockers is opposed by nitrates.
2. Nifedipine + β-blockers. The antianginal effects are additive. Reflex tachycardia due to nifedipine is countered by β-blockers.
3. Nitrates + CCBs—nitrates decrease preload, CCBs reduce after-load and the combination reduces cardiac work load.
4. CCBs + β-blockers+ Nitrates—If the angina is not controlled by 2 drug combinations, 3 drugs can be used. Nitrates reduce preload, CCBs reduce afterload while β-blockers decrease heart rate. This combination is useful in severe angina.

Unstable angina includes:

- Patients with exertional angina developing angina at rest.
- Severe, prolonged anginal attacks
- Angina developing after myocardial infarction.

Such patients with unstable angina are at a high risk of developing MI and need rigorous treatment for its prevention.

MYOCARDIAL INFARCTION (MI)

Classical presentation of MI

- Chest pain : Lasting for hours.
- Sudden severe pain or tightness in chest / with restlessness / with sweating or vomiting.

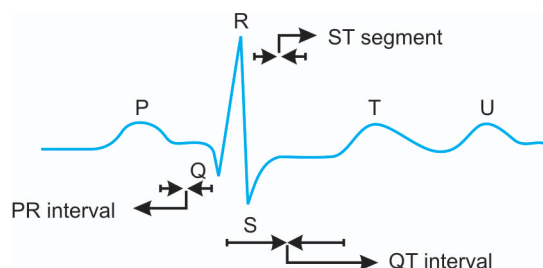


Fig. 7.3.4: Normal ECG

Investigation

ECG (Fig. 7.3.4)

Angina (Fig. 7.3.5)

- ST segment - depression
- T wave inversion or tall, pointed upright

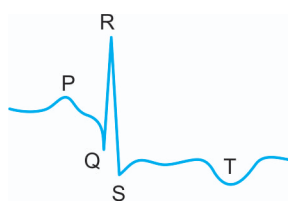


Fig. 7.3.5: T wave inversion

Myocardial Infarction (Fig. 7.3.6)

- ST segment - elevated
- Q wave is broad and deep
- T wave tall/inverted/upright

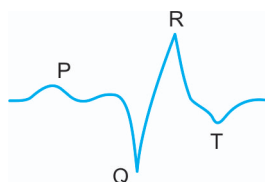


Fig. 7.3.6: Broadening of Q wave

Other Nonspecific test:

- ESR rises above 70 mm in first hour.
- Polymorphonuclear leukocytosis [$20 \times 10^9/L$]

Cardiac Enzymes:

- Within 48 hours of Infarction. Creatinine Kinase (CK): increased up to 24 hours, normal after 48 hours.
- Within 3 days:
 - Rise in AST (Aspartate Aminotransferase)
 - Rise in LDH (rises up to 3–4 days & remain high up to 12 days).
 - Troponin T and Myoglobin rises (high up to 7 days)

[AIM FOR MANAGEMENT OF MYOCARDIAL INFARCTION]

1. Oxygen 60% by face mask/nasal cannula.
2. For treatment of pain/anxiety and apprehension :
 - Diazepam
 - Morphine (10 – 20 mg IV or SC) or Dimorphine (5 – 10 mg IV/SC).
 - + Antiemetic (cyclizine 50 mg IV) or Metoclopramide (10 mg IV).
3. Correction of acidosis (due to lactic acid production)
 - Na-bicarbonate (IV)
4. Thrombolytic therapy (beneficial < 24 hours)
 - Streptokinase or
 - Urokinase or
 - Alteplase
5. Prevention and treatment of arrhythmias :
 - Prophylactic administration of beta blockers: if started immediately, it will also reduces infarct size, continue it for 4 weeks. It will also prevent other complications (myocardial salvage)
 - For tachyarrhythmia: Lidocaine (IV)
 - For bradycardia/block: Electrical pacing or atropine
6. For management of Pump failure:
 - a. Furosemide: If pulmonary wedge pressure is > 20 mm of Hg.
 - b. Vasodilators: Glycerine trinitrate (GTN) IV or ACE inhibitors (captopril)
 - c. Inotropic agent: Dopamine/Dobutamine rarely digitalis.
7. For the prevention of thrombus formation. Heparin (5000 U SC 8 hourly), Low dose heparin reduces deep vein thrombo-embolism
8. For the prevention of remodeling, i.e. cardiomyopathy. Immediate start ACE Inhibitors
9. Prevention and reduction in Risk factors/modification of life style.
10. Secondary prophylaxis: low dose aspirin (60–150 mg/day)

Principles for Treatment of Acute Myocardial Infarction

Before Hospitalization

- For relief of pain
 1. 0.4 mg nitroglycerine sublingually every 5 minutes till pain subsides (max. 3)
 2. IV morphine, 1 mg/min (max. 10 mg) with IV metoclopramide 10 mg.
 3. Oxygen.
- For anti-platelet action: Aspirin 75 to 150 mg once daily.

After Hospitalization

- Absolute bed rest.
- Specific treatment for hypertension.
- ACE Inhibitor (prevent remodeling).
- IV beta blocker (decrease and restrict infarct size) and prevent complications.
- Anticoagulant.
- Thrombolytic therapy (within 12 hours of onset of acute MI).
- Treatment of complications.

- General measures: Diet, exercises, relaxation, bowel care, sedation, etc.

Discharge and secondary prophylaxis:

1. Gradual increase in physical activity (including yoga, walking and exercise therapy).
2. Low dose aspirin
3. ACE inhibitor.
4. Beta blockers
5. Risk factor modification: alcohol, smoking, hypertension, diabetes mellitus, hyperlipidemia and obesity.

Cardiac Arrhythmia and Antiarrhythmic Drugs

Definition: Arrhythmia is an abnormality of the rate, rhythm or site of origin of the cardiac impulse or an abnormality in the impulse conduction.

- Cardiac arrhythmias may be due to abnormal generation or conduction of impulses.
 - Automaticity Defect:** Disturbances of impulse generation may be due to altered normal automaticity or after-depolarization.
 - Conductivity Defect:** In disturbances of impulse conduction, an impulse may re-circulate in the heart and cause repeated activation (re-entry). (Fig. 7.4.1).

Factor responsible for Cardiac arrhythmias: Factors like hypoxia, electrolyte disturbances, trauma, drugs and autonomic influences can cause arrhythmias.

- Dysrhythmias arise because of:
 - delayed after-depolarization, which triggers ectopic beats
 - re-entry, resulting from partial conduction block
 - ectopic pacemaker activity
 - heart block
- Delayed after-depolarization is due to an inward current associated with abnormally raised $[Ca^{2+}]_i$.
- Re-entry is facilitated when parts of the myocardium are depolarized, conduction then depending on the Ca^{2+} -mediated 'slow response'.
- Ectopic pacemaker activity is encouraged by sympathetic activity.
- Heart block results from damage to the AV node or ventricular conducting system.

Clinically, dysrhythmias are divided:

- According to their site of origin (**supraventricular and ventricular**)
- According to whether the heart rate is increased or decreased (**tachycardia or bradycardia**).

Generally, Antiarrhythmic drug acts in two ways:

- Either it reduces the responsiveness of the cell membrane to stimulus and therefore by reducing conduction velocity and abolishes re-entry by converting unidirectional block to bi-directional block i.e. in Figure 7.4.1 D or by
- Terminating re-entry by increasing membrane responsiveness and thereby limits the unidirectional block and normalizing the conduction (Fig. 7.4.1A).

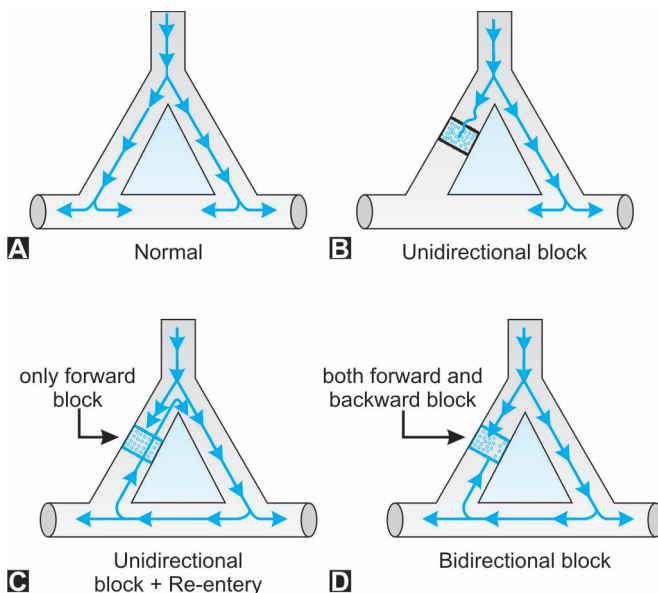


Fig. 7.4.1: Arrhythmia due to conductivity defect

CLASSIFICATION

Based on the cardiac cycle, Vaughan Williams classified antiarrhythmics as follows:

Class I	Sodium channel blockers	
	a. Prolong repolarization	Quinidine, Procainamide, Disopyramide
	b. Shorten repolarization	Lignocaine, Mexiletine, Phenytoin
	c. Little effect on repolarization	Encainide, Flecainide
Class II	β-adrenergic blockers (reduce sympathetic tone)	Propranolol, Acebutolol, Esmolol, etc.
Class III	K⁺ channel blockers (Prolong repolarization)	Amiodarone, sotalol
Class IV	Ca⁺⁺ channel blocker (Prolong conduction) and refractoriness (specially in SA and AV nodes)	Verapamil, Diltiazem

The action of antiarrhythmic drugs can be better understood by knowing the various phases of the cardiac impulse:

Class I: Sodium Channel Blockers**Class IA Drugs (Fig. 7.4.2):**

- Class I A drugs prevent inward sodium movement by blocking Na⁺ channels.
- Depress (slows) phase-0 depolarization and
- Prolong repolarization.
- They prolong APD (Action Potential Duration)
- Also prolong ERP (Effective Refractory Period)
- These drugs have an intermediate rate of association with sodium channels:
- These drugs reduces conduction velocity and shift threshold potential toward 0.

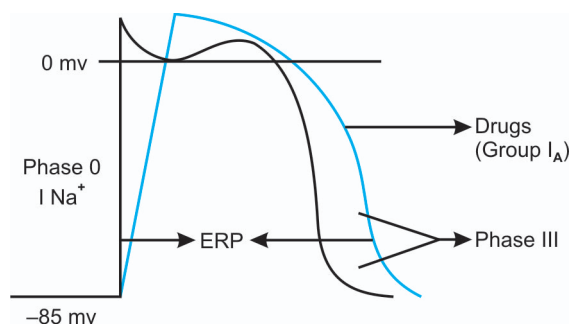


Fig. 7.4.2: AP for I_A group drugs

Quinidine

- It is the D-isomer of quinine obtained from the cinchona bark.
- By blocking Na⁺ channels, it depresses all cardiac propagation of the action potential.
- Quinidine also has vagolytic and α blocking properties. It is also a skeletal muscle relaxant.

- On oral administration quinidine is rapidly absorbed, 90% bound to plasma proteins, metabolised in the liver and excreted in urine.
- Quinidine itself can cause arrhythmias and heart block.
- Other adverse effects includes: Hypotension, nausea, vomiting, diarrhea, hypersensitivity and idiosyncratic reactions.
- Higher doses can cause cinchonism like quinine.

Procainamide

- It is a derivative of the local anesthetic 'procaine'.
- It has the advantages over quinidine that it has weak anticholinergic properties and is better tolerated than quinidine.

Disopyramide

- It has significant anticholinergic (atropine) properties.
- It is sometimes used in patients with recurrent paroxysmal atrial fibrillation occurring in a setting of vagal overactivity.

Uses: Class IA drugs are useful in almost all types of arrhythmias. Quinidine and procainamide are now seldom use, because of their side-effects. Disopyramide is similar to quinidine, and has marked atropine like effects.

Class IB Drugs (Fig. 7.4.3)

- Class IB drugs block the sodium channels and also **shorten repolarization**.
- These drugs also depress (slows) phase '0' depolarization but has little effect.
- They reduces APD (Action Potential Duration)
- They also reduces EPD (Effective Refractory Period)
- These drugs have a rapid rate of association with sodium channels.
- They do not inhibit pace maker depolarization but inhibits the inward sodium current associated with ectopic beat of ventricular arrhythmias (Phenytoin is used only in treatment of digitalis induced arrhythmias)

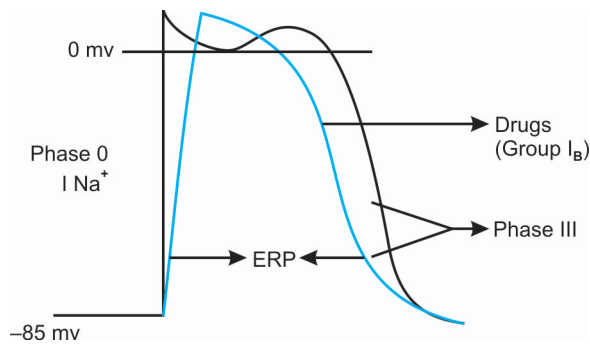


Fig. 7.4.3: AP for I_B group drugs

Lignocaine

- It is a local anesthetic. It suppresses the electrical activity of the arrhythmogenic tissues while the normal tissues are not much affected.
- Given orally lignocaine undergoes high first pass metabolism and has a short $t_{1/2}$, hence used parenterally.
- It may cause drowsiness, hypotension, blurred vision, confusion and convulsions.

Phenytoin: It is an anti-epileptic also useful in ventricular arrhythmias (not preferred due to toxicity) and digitalis induced arrhythmias.

Mexiletine

- It is used as an alternative to lignocaine in ventricular arrhythmias.
- It can be used orally; causes dose related neurologic adverse effects including tremors and blurred vision.

Class IB drugs are useful in:

- Lignocaine is used (intravenously) to treat ventricular tachycardia and prevent ventricular fibrillation during and immediately after myocardial infarction.
- Phenytoin has been used to treat digoxin-induced dysrhythmias, but this is obsolete.

Choice of drugs in cardiac arrhythmias

Arrhythmias	Causes	Treatment
Sinus tachycardia	↑ sympathetic tone, fever, thyrotoxicosis	Treat the cause if severe—propranolol
Atrial extrasystoles	Excess caffeine, nicotine, alcohol	Treat the cause: Reassurance If severe: propranolol/disopyramide
Atrial flutter/fibrillation	Rheumatic heart disease, cardiomyopath, hypertension	Cardioversion Propranolol/quinidine/disopyramide/digitalis
PSVT		Vagal maneuvers like carotid massage Verapamil/adenosine/ β -blockers
Ventricular ectopics	Normal heart—benign; also in cardiomyopathy, ischemic, digitalis induced	β -blockers Lignocaine

Contd...

Class IC Drugs (Fig. 7.4.4):

- Class IC drugs are the most potent sodium channel blockers.
- These drugs have slow rate of association with sodium channels.
- These drugs depresses (slows) phase '0' depolarization very rapidly (markedly)
- They do not produce any change in APD and ERP.
- These group of drugs should be kept reserved for resistance cases.
- In (CAST) Cardiac Arrhythmic Suppression Trial, this group of drug were found to be **Pro-arrhythmic**
- Because of the risk of cardiac arrest, sudden death and other adverse effects, they are not commonly used. They may be used in treatment of ventricular arrhythmias.

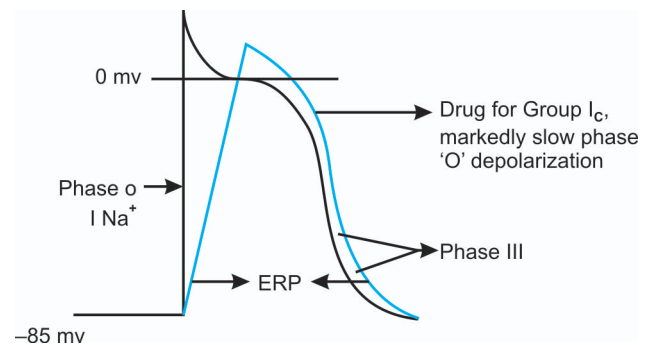


Fig. 7.4.4: AP for I_C group drugs

- **Flecainide** reduces ventricular ectopics, but increases mortality after myocardial infarction.
- It is sometimes used for paroxysmal atrial fibrillation in patients with disabling symptoms, and for some patients with recurrent tachyarrhythmias associated with abnormal conducting pathways (e.g. Wolff-Parkinson-White Syndrome).
- **Propafenone:** also possesses beta blocker and calcium channel property.

Contd...

Ventricular tachycardia	Organic heart disease and ventricular dysfunction, drug-induced	Cardioversion Lignocaine
Ventricular fibrillation	Acute MI, organic heart disease, surgical trauma, drug-induced	Cardioversion Lignocaine Class IA drugs for prevention
Digitalis induced tachyarrhythmias	Digitalis toxicity	Phenytoin/Potassium/Lignocaine

Class II Drugs **β - Adrenergic Blockers:**

- Eg. Propranolol, sotalol, Nadolol, Timolol, Pindolol, Atenolol, Acebutolol, Metoprolol, Esmolol.
- This group of drugs diminishes phase IV of depolarization.
- They reduce the automaticity of SA node.
- These drugs prolong (slow) AV Conduction.
- They also prolong AV nodal refractory period.
- They also reduce heart rate and contractility.

Propranolol

- It exerts antiarrhythmic effect due to blockade of cardiac receptors (in high doses has membrane stabilizing activity).
- Propranolol is used in the treatment of supraventricular arrhythmias especially those associated with exercise, emotion or hyperthyroidism.

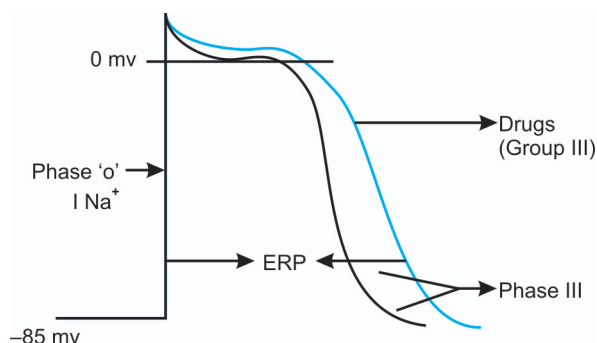
Esmolol

- It is given intravenously, is rapid and short-acting and
- It can be used to treat arrhythmias during surgeries and other emergencies.

Sotalol: It is a β -blocker also prolongs the action potential duration and is often preferred when a β -blocker is needed.

Class III Drugs (K^+ Channel Blockers) (Fig. 7.4.5)

- This group of drugs have no effect on phase '0' depolarization.
- These drugs prolong the action potential duration (APD) and effective refractory period (ERP) by blocking the potassium channels.

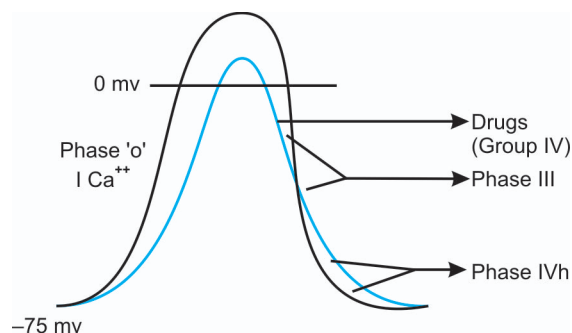
**Fig. 7.4.5:** AP for class III group drugs**Amiodarone**

- It is a powerful antiarrhythmic agent.
- In addition to prolonging action potential duration, it also blocks β adrenergic receptors and sodium channels.
- It has adverse effects like heart block, cardiac failure, hypotension, hypothyroidism, pulmonary fibrosis and hepatotoxicity.
- It is used only in resistant cases of chronic ventricular arrhythmias and to prevent recurrence of atrial fibrillation and flutter.

Bretylium: It is an adrenergic neurone blocker used in resistant ventricular arrhythmias.

Class IV Drugs (Ca^{++} Channel Blockers) (Fig. 7.4.6): Calcium channel blockers inhibit the inward movement of calcium resulting in reduced contractility, automaticity and AV nodal conduction.

- They reduce SA nodal activity – (automaticity)
- Prolong AV nodal refractory period
- Also slows phase IV spontaneous depolarization and slows conduction in the tissue.

**Fig. 7.4.6:** AP for class IV group drugs

Verapamil and diltiazem have prominent cardiac effects. Verapamil is the main drug. It is used;

- To prevent recurrence of paroxysmal supraventricular tachycardia (SVT)
- To reduce the ventricular rate in patients with atrial fibrillation (especially if inadequately controlled with atrial fibrillation with Wolf-Parkinson-White or a related pre-excitation syndrome)

- Verapamil was previously given intravenously to terminate paroxysmal supraventricular tachycardia (SVT); it is now seldom used for this because adenosine is safer.
- They are ineffective and dangerous in ventricular dysrhythmias.

Miscellaneous (Adenosine and digoxin)

- Both drugs prolong ERP in AV node
- Both drugs reduces conduction velocity.
- Uses: In treatment of supraventricular tachycardia, Atrial flutter, and atrial fibrillation.

Adenosine

- It is a purine nucleotide having rapid and short antiarrhythmic action.
- Given IV it suppresses automaticity, AV conduction and dilates the coronaries.
- Adenosine is the drug of choice for acute termination of paroxysmal supraventricular tachycardias (PSVT).
- It is superior to verapamil and even safer because it has no negative inotropic effect and therefore can be used in ventricular arrhythmia.
- Adverse effects are nausea, dyspnea, flushing and headache but are of short duration.

Shock and Its Management

Definition: In shock there is failure of circulatory system to maintain adequate cellular/ tissue perfusion, therefore ultimately leads to (a) decrease in oxygen delivery and (b) decrease in nutritional supply to tissue.

- Shock represents a failure of blood flow rather than a fall of BP and the diagnosis of shock is based, not on the level of arterial blood pressure but on the signs and symptoms of inadequate perfusion of vital organs.
- Arterial blood pressure and cellular perfusion are dependent on:
 - Cardiac factor: cardiac output, stroke volume and heart rate.
 - Vascular factor: sympathetic, endothelial nitric oxide.
 - Humoral factor: circulating mediators, i.e. Angiotension II, renin, vasopressin, prostaglandins, kinins, etc.
 - Microcirculating factors:
 - Local metabolite, pH
 - Hydrostatic pressure.
- Symptoms of sympathetic over activity of tissues are generally seen-like pallor, sweating, cold extremities and tachycardia. Shock may be:
 1. *Hypovolumic shock*: Decreased fluid volume due to sudden loss of plasma or blood as in hemorrhage, burns or dehydration a (fluid depletion): results in hypovolemic shock.
 2. *Cardiogenic shock* is also called as myopathic shock. It is due to failure of heart as a pump as in myocardial infraction.
 3. *Septic shock* (distributive shock) is precipitated by severe bacterial infection. It may be due to release of bacterial toxins.
 4. *Neurogenic shock* is due to venous pooling as following spinal anesthesia, abdominal or testicular trauma.
 5. *Anaphylactic shock*: Type I hypersensitivity reaction causing release of massive amounts of

histamine which is triggered by antigen-antibody reaction.

6. *Distributive shock: septic shock, toxic product: anaphylactic drugs, anaphylaxis, neurogenic and endocrinal shock, endocrinal shock.*
7. *Extracardiac obstructive shock: pericardial tamponade, pulmonary embolism, severe pulmonary hypertension, etc.*

Type of Shocks (in detail) (Fig. 7.5.1): Shock is classified according to its etiology and is of following types:

Hypovolumic Shock (Fig. 7.5.2)

- This results from external or internal loss of blood, plasma or water following hemorrhage, trauma, burns (extensive) protracted vomiting or diarrhea.
- In this, the major hemodynamic abnormality is compensatory vasoconstriction, decreased venous return and a low cardiac output due to reduced plasma volume.
- *Therapy consists of appropriate fluid replacement, using saline, plasma or blood and correction of acidosis. Extreme vasoconstriction may be diminished by using alpha-adrenoceptor blocking agents like phentolamine or phenoxybenzamine.*

Cardiogenic Shock

- It is due to acute myocardial infarction.
- There is failure of the heart as a pump. The hemodynamic pattern usually consists of reduced cardiac output and normal or increased peripheral resistance.
- *Therapy consists of relief of pain and anxiety, oxygen administration to antagonize tissue hypoxia and acidosis, use of thrombolytic agents and anticoagulants, vasopressor or vasodilator drugs.*

Septic Shock

- It occurs during the course of Gram –tive or less commonly Gram +tive bacterial infection.

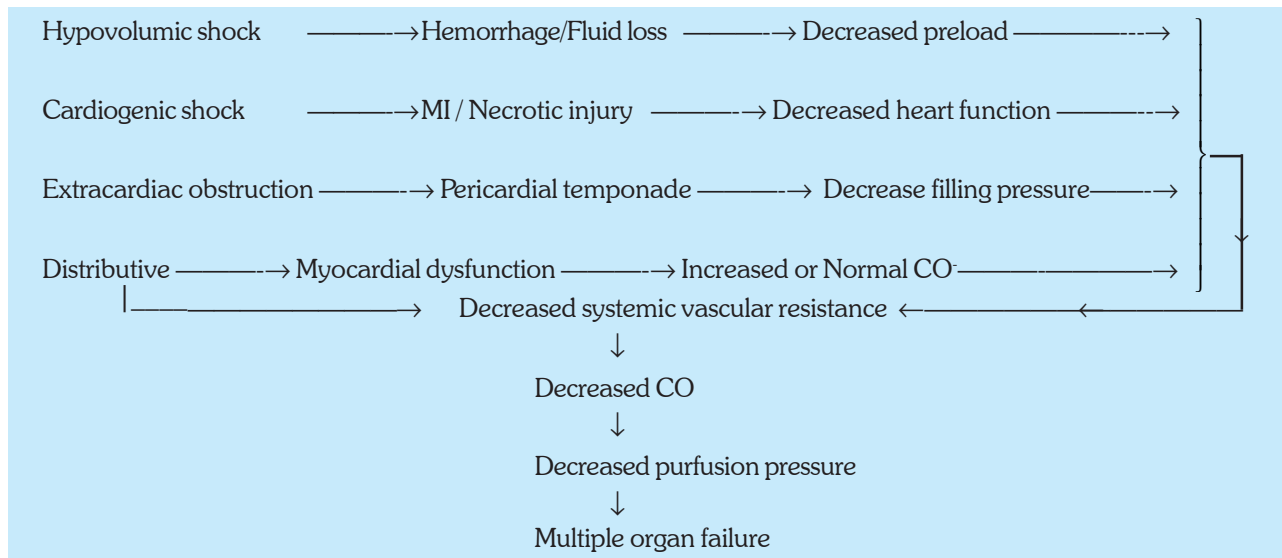


Fig. 7.5.1: Various types of shocks and their final outcome

- Treatment consists of intensive antibiotic therapy, maintenance of adequate circulating volume by fluid replacement, use of vasopressor drugs-dopamine, dobutamine and corticosteroids administration to suppress the systemic reaction to endotoxins.

Anaphylactic Shock

- It is due to hypersensitivity reaction and is characterized by extreme vasodilatation, increased capillary perme-

ability, exudation of fluid in the tissues, angioneurotic edema and bronchoconstriction.

- Treatment consists of administration of adrenaline, antihistaminics, corticosteroids, oxygen and fluid replacement.

Shock of Any Type Needs Immediate Treatment

- The cause should be identified and treated.
- Symptomatic management is very important maintain BP and plasma volume.
- Correct the acid base and electrolyte disturbances.
- Ensure adequate urine output.

Aim of Therapy

The two basic aims in the therapy of shock are :

1. To eliminate the initiating cause and
2. To correct the hemodynamic derrangement.

To correct the hemodynamic dearrangement, it is first necessary to ensure adequate fluid replacement and venous return, regardless of cause.

- In shock where the BP is inadequate to perfuse vital organs, it is treated by using drugs having positive inotropic and vasoconstricting actions like noradrenaline, dobutamine, metaraminol, etc. The drugs are given in the smallest effective dose for shortest time, to avoid excessive vasoconstriction.
- In shock where the central arterial pressure is sufficient, but blood flow to viscera is reduced due to vasoconstriction, drugs having positive inotropic effect and vasodilating action are indicated-combinations of no-radrenaline and phentolamine or dopamine with iso-prenaline may be effective.

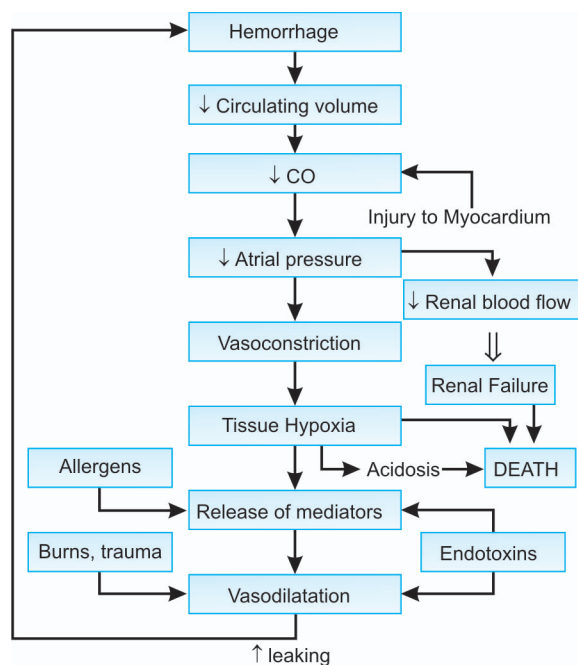


Fig. 7.5.2: Pathogenesis of hypovolumic shock

Drugs used in the Therapy of Shock

- **Blood loss:** Blood, fluids, plasma expanders, dopamine, alpha blockers
- **Acute myocardial infarction:** Analgesics (morphine), dopamine, dobutamine, thrombolytic agents, anticoagulants.
- **Anaphylactic shock:** Adrenaline, corticosteroids.
- **Septic shock:** Antibiotics, fluids, corticosteroids.

Sympathomimetic Amines. These drugs maintain perfusion of the vital organs by one or more of the following mechanisms:

1. Increasing myocardial contractility, which increases cardiac output provided the venous return is adequate.
2. Constricting the capacitance vessels-venules, and preventing pooling of blood in the veins.
3. Dilating arterioles in the vital organs.

The various sympathomimetics used in the treatment of shock are:

- **Adrenaline:** It is used mainly in the treatment of anaphylactic shock.
- **Noradrenaline:** It raises the perfusion pressure and the cardiac output in patients of shock with very low peripheral resistance.
- **Dopamine:** It is employed in the management of cardiogenic shock, septic shock and traumatic shock, alone or in combination with an alpha-adrenoceptor blocking agent. It stimulates heart and increases cardiac output by acting on cardiac beta receptors and improves renal and mesenteric blood flow by acting on dopamine receptors.
- **Dobutamine:** It acts mainly on β_1 receptors with fewer vascular effects. It is used for short-term therapy

of severe CCF and in patients following cardiac surgery, to increase cardiac output.

Other sympathomimetic agents used are metaraminol methoxamine, phenylephrine.

Alfa-adrenoceptor blocking agents: Phenoxybenzamine has been used in traumatic or surgical shock, after adequate replacement of fluid volume. It reduces the vasoconstriction produced by the reflex release of noradrenaline and it

- a. Prevents the harmful effects of vasoconstriction on microcirculation
- b. Permits rapid administration of IV fluid without increasing central venous pressure.

Dextran and other plasma expanders: High molecular weight dextran (MW 110,000) and Low molecular weight dextran (MW 40,000) are used in the emergency treatment of hypovolemic shock. They expand plasma volume temporarily, by exerting osmotic pressure and drawing fluid into the vascular space, thus improving blood flow.

Glucagon: It increases myocardial contractility and improves the hemodynamic status of patients in acute cardiac failure following cardiac surgery, shock following myocardial infarction and in the treatment of beta adrenoceptor blocker overdose.

Corticosteroids: These are useful in the management of anaphylactic shock, septic shock and the shock due to acute adrenal insufficiency. Proper antibiotic coverage should be done if it is used in septic shock.

Oxygen: It is used in patients of cardiogenic shock having dyspnea or cyanosis due to arterial hypoxemia.

Plasma Expanders

- Plasma expanders are the high molecular weight substances which exert osmotic (colloidal) pressure.
- In emergency, like burn and severe blood loss (hemorrhage), immediate volume replacement is required. In such situations plasma expanders are used. They restore the intravascular volume, when infused intravenously.
- An ideal plasma expander should exert oncotic pressure equivalent to plasma, remain in circulation, be long-acting, non-antigenic, anti-allergic, stable, pharmacologically inert, i.e. should not affect any visceral function adversely, cheap and easily available.
- Plasma expander can be classified as **colloids** and **crystalloids**:

Colloids	Crystalloids
1. Human albumin	1. Normal Saline
2. Dextran,	2. Dextrose.
3. Gelatin polymer,	
4. Hydroxyethyl starches	
5. Polyvinyl pyrrolidone.	

COLLOIDS

Human albumin:

- Obtained from pooled human plasma
- 100 ml of 20% human albumin solution = 400 ml of fresh frozen plasma = 800 ml of whole blood.
- Used in acute cardiac failure, shock and hypoproteinaemia and burns. Occasionally, febrile reaction may occurs.

Dextrans:

- Polysaccharide obtained from sugar. (Dextran 70 mol. wt. 70,000 and dextran 40 mol. wt. 40,000) are commonly used.

- Oncotic pressure of dextran is similar to that of plasma protein and they persist in the plasma with an effective half life of about 24 hours.
- Occasionally it can precipitate acute oliguric renal failure.
- Allergic reactions are also very common.
- Infused in quantities larger than 1 liter (20 ml/kg) per day.

Gelatin products (polymer)

- They have a mol. wt. of 30,000 and a duration of action of 12 hours.
- Hemacel: is the one of such polymer of degraded gelatin available commercially.
- Allergic reactions are rare, occasionally urticaria and flushing can occur.
- Bronchospasm and fall in blood pressure can also occur.

Hydroxyethyl starch (Hetastarch)

- Molecular weight 450,000.
- Maintains blood volume for a long period.
- Allergic reactions are rare.
- Does not cause acute renal failure or coagulation disturbances.

Polyvinyl pyrrolidone (PVP)

- It is a synthetic, water soluble and hydrophilic polymer.
- Molecular weight lies between 35,000 and 40,000.
- It is administered intravenously. Its excretion is very fast.
- It is not preferred due to various disadvantages like-it provokes histamine release and interferes with blood grouping.
- It may interfere with antibody formation.

CRYSTALLOIDS

Normal saline

- 0.9% normal saline is the most widely used IV preparation.

- Infusion of 1 liter of normal saline raises the blood volume by about 300 ml.
- It is mainly useful to replace lost sodium, water and chloride.
- It can also be used as a vehicle for giving IV drugs by drip.
- Rapid administration may produce pulmonary edema.
- Sometime febrile reaction may be produced.

Dextrose

- 5% solution in water.
 - Infusion of 1 liter of dextrose in water raises the blood volume by about 100 ml only.
- It supplies nutrition.
 - It is very useful particularly when renal function is impaired.
 - It can also be used as a vehicle for giving IV drugs (specially nor adrenaline) by drip.

Uses of Plasma Expanders

- These are used as plasma substitutes in hypovolemic shock, burns and extensive fluid loss as an emergency measure to restore plasma volume.
- In general colloids are superior to crystalloids in maintaining blood volume and in minimizing the shock level, but they are costly.



S E C T I O N

8

Endocrinology

Hypothalamic and Pituitary Hormones

Endocrinal Glands: The endocrinal glands are the small islands of tissues in various parts of the body, which secrete a substance directly into blood stream (ductless-glands) and circulate in the body, called **hormones**.

- These hormones act at sites located away from their place of origin, by interacting with specific receptors, thus producing their effects.
- Most of these hormones have been isolated and their structure determined, which has made it possible to prepare them synthetically and by recombinant DNA technology.

Hormones are classified into:

- **Hypothalamic hormones:** They are secreted by the median eminence of the hypothalamus and are regulating the secretion of hormones from anterior pituitary (AP) (Fig. 8.1.1).

Releasing hormones: [from **Basophilic cells**]

1. **TRH** (Thyrotropin releasing hormone)
2. **CRH** (Corticotropin releasing hormone)
3. **FSH-RH** (Follicle stimulating releasing hormone)
4. **LH-RH** (Luteinizing hormone releasing hormone)

Inhibitory hormones + Releasing hormones (mix): [from **Acidophilic cells**]

1. **PRH** (Prolactin releasing hormone) or **PRF**
PIH (Prolactin inhibiting hormone)
 2. **SRH** (Somatotropin releasing hormone) or **GHRH** (Growth hormones releasing hormones).
GH-RIH (Somatostatin) Inhibitory
 3. **MS-RH** (Melanocyte stimulating releasing hormone)
MS-IH (Melanocyte stimulating inhibitory hormone)
- **Pituitary hormones** (Fig. 8.1.1) – They are released by:
 - a. **Anterior pituitary** (Adenohypophysis) - which exercise a controlling influence over rest of the endocrine glands:
 1. **GH** (Growth hormone) or Somatotropin
 2. **Prl** (Prolactin)
 3. **ACTH** (Adreno-cortico tropic hormone)

4. **TSH** (Thyroid stimulating hormone)

5. **FSH** (follicle stimulating hormone)

6. **LH** (luteinizing hormone)

7. **MSH** (Melanocyte stimulating hormone)

- b. **Posterior pituitary** (Neurohypophysis) – which affect the uterus and water conservation.

1. **ADH** (Anti-diuretic hormone) or *vasopressin*

2. Oxytocin

• **Hormones affecting metabolism**

Thyroid hormones:

- Thyroxin (T_4)
- Tri-iodothyronin (T_3)
- Calcitonin (It reduces plasma calcium level)

Parathyroid hormones:

- Parathormones (It increases plasma calcium level)

Pancreatic hormones:

- Insulin
- Glucagons
- Somatostatin
- Pancreatic polypeptide

Adrenal hormones:

A. Cortex:

Glucocorticoids: Hydrocortisone, Prednisolone, and Dexamethasone

Mineralocorticoids: Aldosterone and Fludrocortisone

Sex Steroids: Dehydro-epiandrosterone

B. Medulla

Adrenaline and Nor-adrenaline

• **Hormones affecting the reproductive system –**

Female and male sex hormones:

1. Androgen (testosterone)
2. Estrogen (estradiol)
3. Progestin (progesterone).

• **Placental Hormones**

1. Chorionic gonadotropins
2. Progesterone

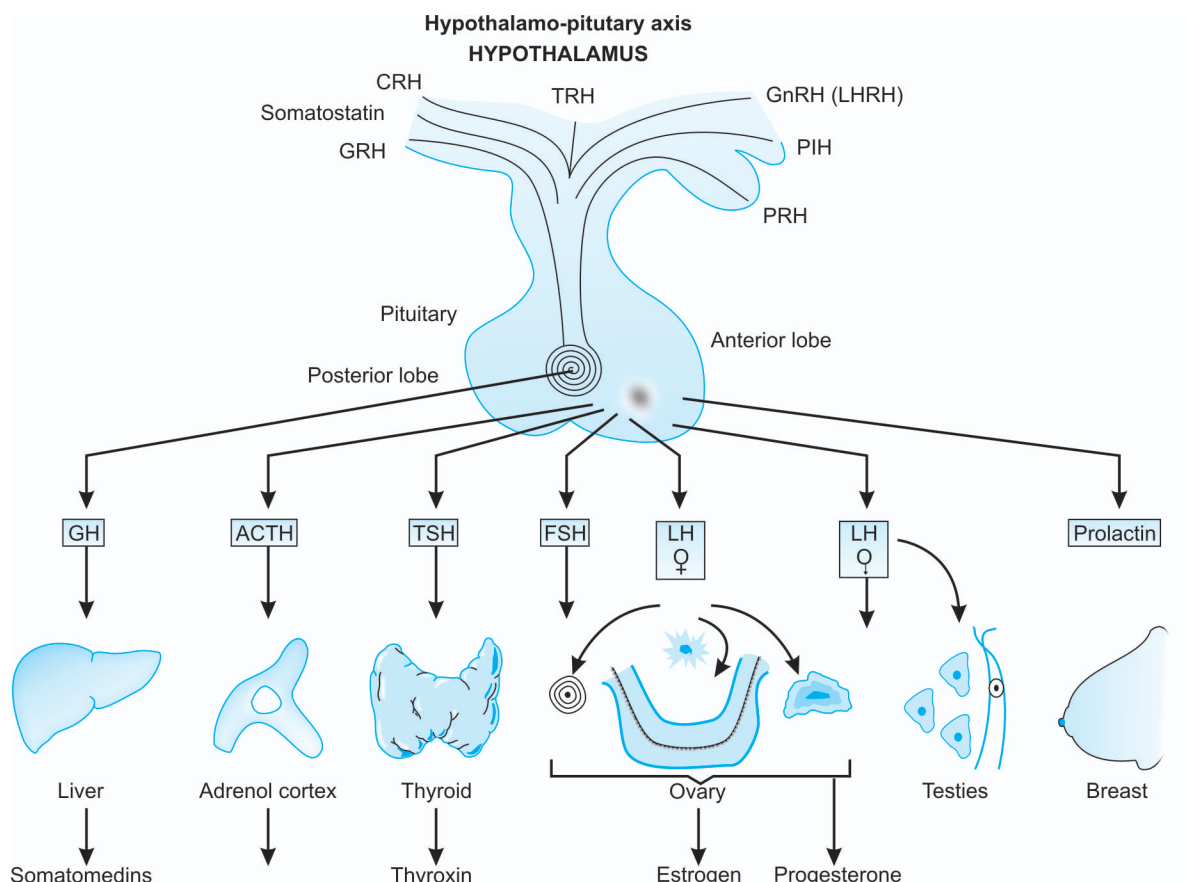


Fig. 8.1.1: Hypothalamo-pituitary axis (gland) and the hormones secreted by them

3. Estrogen
4. Placental lactogen
5. Prolactin
6. Chorionic thyrotropins, etc.

- **Local Hormones Autacoids:** Discussed previously

Hormones may be steroids or peptides:

1. **Steroidal hormones:** They need multiple enzymes in their biosynthesis. They have relatively longer half life, the binding proteins are present and their peripheral transformations are common.
2. **Peptide hormones:** Their synthesis take place through single protein, prohormone. They are having short half life, binding proteins are very rare and peripheral transformations do not occur.

Sites and Mechanism of Action of Hormones:

A. At cell membrane receptors:

1. **Through AC = Adenyl Cyclases/cAMP/pk_A generation:**

Primary messenger: **Hormone**

Secondary messenger: **cAMP**

Tertiary messenger: **Ca⁺⁺**

Examples: Adrenalin, Glucagons, TSH, FSH, LH, PTH, ACTH, GH, Calcitonin.

2. **Through IP₃/DAG/pk_C generation:**

Examples: ADH, Vasopressin, Insulin.

B. At cytoplasmic receptors:

Examples : Steroid hormones : Glucocorticoids, Mineralocorticoids, Estrogen, Progestin.

Hormone bind with cytoplasmic receptors
 ↓
 Expose its DNA binding domain
 ↓
 Migrate to nucleus and bind with specific gene
 ↓
 DNA mediated RNA synthesis
 ↓
Synthesis of functional protein

C. At nuclear receptors:

Hormones directly penetrate the nucleus → Combined with receptor → Alter DNA – RNA mediated protein synthesis.

Examples: Thyroid hormones: Thyroxin, Triiodothyronin.

HYPOTHALAMIC HORMONES: The secretion from anterior pituitary (AP) is regulated by hormones released from the hypothalamus, which reach the pituitary through blood stream. These include:

Thyrotropin Releasing Hormone (TRH): It is secreted by the hypothalamus, stimulates the release of TSH from the anterior pituitary. Protirelin is a synthetic TSH.

Corticotropin Releasing Factor (CRF): It releases ACTH and β -endorphins from the anterior pituitary. It is used in diagnostic tests in Cushing's disease (adrenocortical insufficiency).

Gonadotrophin Releasing Hormone (GnRH): It causes release of follicle stimulating hormone (FSH) and Luteinizing hormone (LH) from AP. Synthetic GnRH is called Gonadorelin. Analogues of GnRH have been developed.

- **Agonists** – buserelin, leuporelin, goserelin and nafarelin. Given SC in a pulsatile fashion, with an infusion pump, they stimulate gonadotropin release and are used to induce ovulation. When given continuously, by SC injection or as nasal spray or as depot preparation, they inhibit gonadotropin release and are useful in endometriosis, precocious puberty, advanced prostatic cancer and polycystic ovary syndrome.
- **Antagonists** – danazol and gestrinone – inhibit gonadotropin release and are used in the treatment of endometriosis, menorrhagia and gynecomastia in males.

Prolactin releasing factor (hormone): Causes release of prolactin from AP. Prolactin release inhibiting factor (dopamine) – inhibits the release of prolactin from AP.

Growth hormone releasing hormone: It stimulates anterior pituitary to secrete growth hormone. It is used in diagnostic tests of growth hormone deficiency.

Somatostatin [SRIH]: It is growth hormone release – inhibiting hormone present in the hypothalamus, parts of the CNS, pancreas and in gastrointestinal tract. It inhibits secretion of GH, TSH, Prl, insulin, glucagons and all gastrointestinal (gastric and pancreatic) enzymes. It causes vasoconstriction in GIT. But it is very short-acting. *It is utilized for controlling esophageal ulcer bleeding.*

Octreotide [Octrinide]: It is the synthetic analog of somatostatin which is longer acting and is indicated in:

Acromegaly, carcinoid tumors, bleeding esophageal varices, refractory diarrhea and acute pancreatitis.

ANTERIOR PITUITARY HORMONES: The pituitary gland, under the influence of the hypothalamus secretes many hormones which either control the secretion of other glands or directly act on the target tissues. These are peptides and act by binding to specific receptors present on the target cells.

Growth Hormone (GH)

- It is a peptide, stimulates the growth of all organs except brain and eyes.
- It increases the uptake of amino acids by the tissues, promotes protein synthesis and positive nitrogen balance.
- It (GH) **promotes utilization of fat** by causing **lipolysis** in adipose tissue and reduces glucose uptake by skeletal muscles. It induces glycogenolysis in liver leads to hyperglycemia. It brings about linear growth.
- These anabolic actions are mediated by somatomedins or insulin-like growth factors (IGF₁) produced in the liver.

The secretion of growth hormone is regulated by GHRH and somatostatin (GHRH). See Fig. 8.1.2.

GH deficiency in children results in **dwarfism** while excessive production results in **gigantism** in children and **acromegaly** in adults.

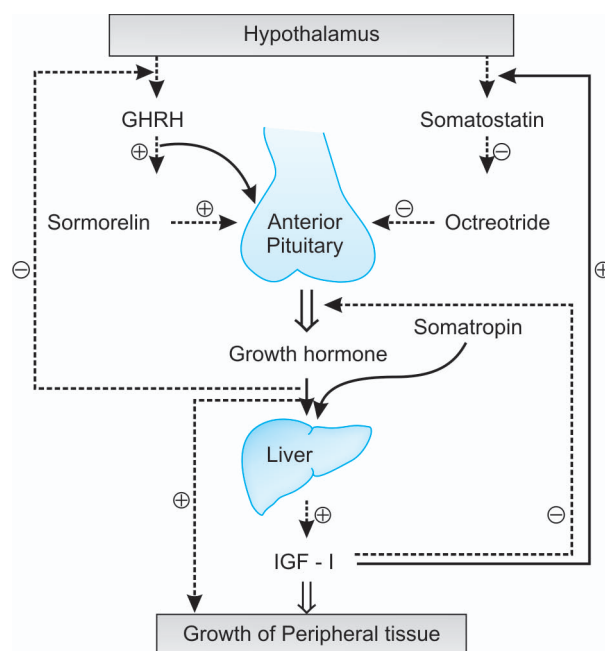


Fig. 8.1.2: Control of growth hormone secretion and its action

Indication of GH

- **GH deficiency:** Replacement therapy with GH deficient children brings about normal growth (treatment of pituitary dwarfism). It can also be used in GH deficient adults.
- Other conditions GH has been tried in:
 - Renal failure
 - Bone marrow hypoplasia (osteoporosis)
 - Juvenile spontaneous hypoglycemia
 - Burn and trauma.

Preparations

- From cadaver pituitary (high chances of fetal viral infection transmission)
- DNA recombinant technology: **Somatrem and Somatropin**
- Dose: **0.06 – 0.16 U/Kg.**

Prolactin

- It causes secretion of crops glands of pigeon.
- This peptide hormone promotes the growth and development of breast during pregnancy. It stimulates milk production along with other hormones like estrogens and progestins.

Prolactin: It is responsible for:

- Proliferation and differentiation of mammary tissue during pregnancy.
 - Control of milk production during lactation.
- Prolactin act upon the estrogen and progesterone primed mammary glands (**lactogenic action**). While 'let down' or flow of milk is being caused by **Oxytocin**.

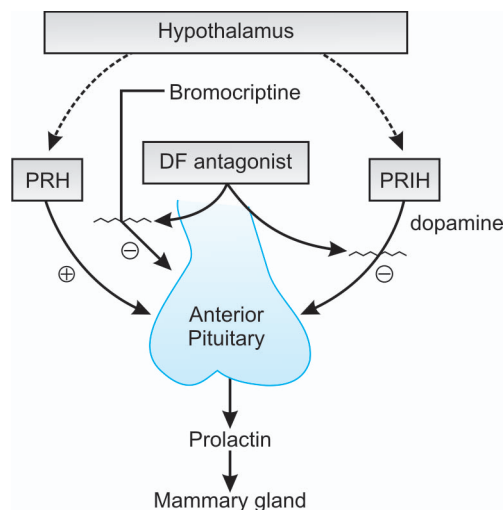


Fig. 8.1.3: Control of prolactin secretion and drugs that modify it

Regulation of Secretion (Fig. 8.1.3)

- Suckling is the principal stimulus for prolactin secretion.
- Estrogens and **dopamine antagonists** like *Chlorpromazines, metoclopramide and haloperidol*, etc. also stimulate prolactin-release.
- Reserpine and methyl dopa, depletes DA, causes prolactin release causes hyper-prolactinemia, It may leads to development of **Gynecomastia in males**.
- **Stress, exertion and hypoglycemia** all stimulate prolactin secretion.
- Dopaminergic agonists like: **DA, Bromocriptine, apomorphine, etc. reduces plasma prolactin level.**
- Deficiency results in **lactation failure** while excess prolactin results in **galactorrhea**

Hyper-prolactinemia

- In females:** Galactorrhea, amenorrhea and infertility syndrome.
- In males:** Loss of libido, depressed fertility and gynecomastia.

Factors responsible for Hyper-prolactinemia

- Hypothalamic disorders.
- Increase in the concentration of anti-dopaminergic drugs.
- Prolactin secreting tumors.
- Hypothyroidism.

Important Note: Prolactin is not used clinically.

Bromocriptine (Potent dopaminergic agonist).

Bromocriptine is an ergot derivative with dopamine agonistic properties.

- It reduces Prl release from pituitary.
- Increases GH release.
- Levodopa like action in CNS that's why used in the treatment of parkinsonism.
- It can produces nausea and vomiting through (CTZ receptor).
- It may reduces blood pressure and produces hypotension.
- It also reduces GIT motility.
- It is mainly excreted in bile.

Clinical use of Bromocriptine

- To prevent lactation without causing pain or engorgement of the breast, as well as to suppress established lactation; it is more effective than estrogens in this latter action.
- To treat galactorrhea, i.e. non-puerperal lactation due to excessive prolactin secretion.
- To treat prolactin-secreting pituitary tumors (prolactinomas).

- In the treatment of parkinsonism (levo dopa like action and of acromegaly).
- Also found to be helpful hepatic coma.

Adverse effect: Postural hypotension and behavioral alteration.

Adrenocorticotrophic Hormone (Corticotropin, ACTH) (Fig. 8.1.4)

ACTH: It stimulates adrenal cortex to increase synthesis (production) and release of **glucocorticoids**, *mineralocorticoids*, and *androgens*.

- Site of action of ACTH: Zona fasciculata and zona reticularis
- Regulation: negative feedback mechanism.
- The production of **Aldosterone** from zona glomerulosa is independent of ACTH action.
- ACTH leads to reduced excretion of Na^+ → leads to edema.
- It also increases excretion of : Uric acid, K^+ , Hydroxy-corticosteroid.

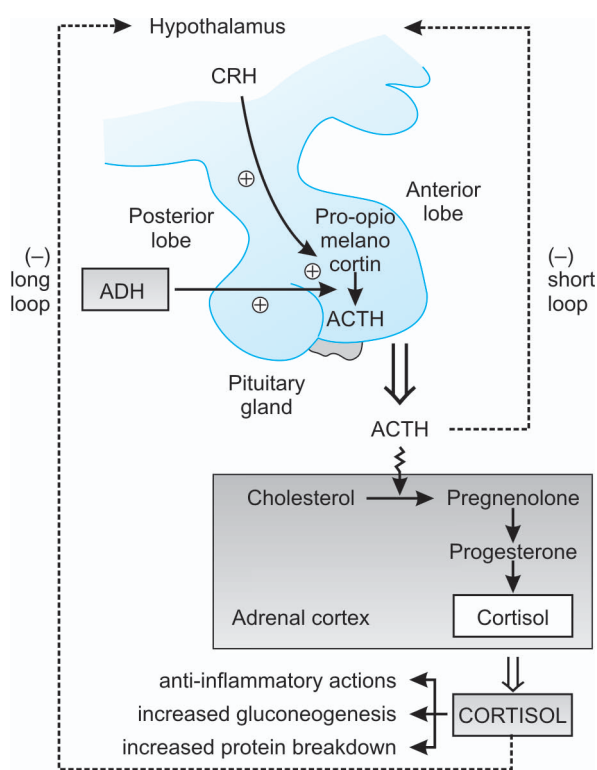


Fig. 8.1.4: Secretion and action of ACTH

Therapeutic Uses:

- Diagnostic use to determine the cause of adrenal insufficiency, i.e. Pituitary origin or due to adrenal failure.

- Use intermittently to avoid adrenaline insufficiency and atrophy as a result of long-term steroidal use.
- Therapeutically it is used for the treatment of : Status asthmatics, anaphylactic shock, rheumatic and collagen disease.
- It is also found to be beneficial in: Multiple sclerosis, myasthenia gravis, ulcerative colitis, infantile convulsions, etc.

Contraindications

- Allergic reactions
- Tuberculosis.
- Azotemic nephritis
- Acute psychosis.
- Peptic ulcers
- Diabetes and heart failure.

Preparations: Short and long acting (20 – 40 U IM/SC)

Synthetic ACTH: Tetraco-sactrin.

Thyroid-stimulating Hormone (TSH, Thyrotropin)

- Thyrotropin stimulates the production and secretion of thyroid hormones and thus regulates thyroid function.
- Regulation: negative feedback mechanism.
- It causes hyperplasia, hypertrophy, and increases blood supply of thyroid glands.
- It increases iodine trapping by thyroid gland
- It increases organification and
- Also increases endocytotic uptake of thyroid colloid by follicular cells.

Pathological involvement

- High TSH: Hyperthyroidism (*Grave's disease*).
- Low TSH: Hypothyroidism (*myxoedema*).

Use: Only diagnostic as well as also used to increase the radioactive iodine uptake in thyroid carcinoma.

Gonadotropins [FSH] and [LH]

Follicle stimulating hormone (FSH) and luteinizing hormone (LH) – produced by the anterior pituitary; regulate gonadal function. See Fig. 8.1.5.

• FSH

- **In females FSH** is responsible for the **development of ovarian follicle**, development of **ovum** and also stimulate ovarian **steroidogenesis** (estrogens and progesterone synthesis).
- **In men FSH** promotes spermatogenesis and growth of seminiferous tubules.

• LH

- **In females LH** is responsible for **ovulation** and later it maintains the corpus luteum. It is also responsible for secretion of progesterone

- In males LH is responsible for **testosterone secretion** and maintenance of **ICSH**.

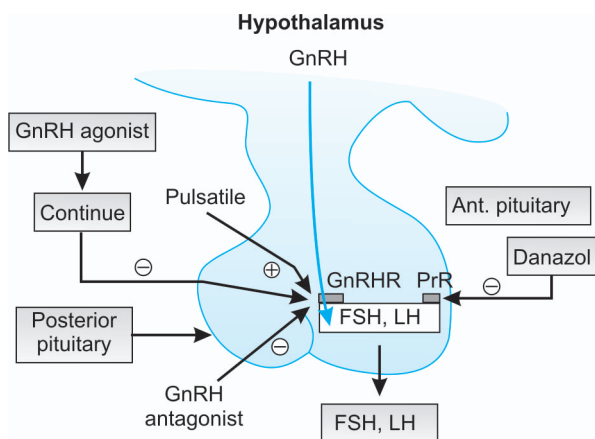


Fig. 8.1.5: Regulation of FSH and LH secretion

- Both FSH and LH act in harmony and follow cyclic pattern in female, characterized by human menstrual cycle (28 days).
 - Follicular phase: High frequency and low amplitude
 - Luteal phase: Low frequency and high amplitude, additionally
 - Inhibin (from testis and ovaries): Inhibit FSH release.
 - Dopamine: Inhibit LH release.
- **Human Menopausal Gonadotropins (HMG): (menotropin)**
 - Obtained from the urine of menopausal females and it mainly act as **FSH**.
- **Human Chorionic Gonadotropins (HCG)**
 - Obtained from the urine of pregnant female and it mainly act like **LH**.

Therapeutic Uses of Gonadotropins (Gns)

- Gonadotropin deficiency induced infertility in males.
- Un-descended testes.
- Secondary amenorrhea and infertility in females.
- In the treatment of habitual abortion.
- In vitro* fertilization to precisely time the ovulation.

Posterior Pituitary Hormones: Posterior pituitary secretes **oxytocin** (see drugs acting on uterus) and **Antidiuretic hormone (ADH, vasopressin)**. The main stimuli for the release of ADH are an increase in plasma osmolarity and a decrease in circulating blood volume (Fig. 8.1.6).

- There are two types of vasopressin receptors – V_1 and V_2 . V_2 receptors mediate reabsorption of water in the

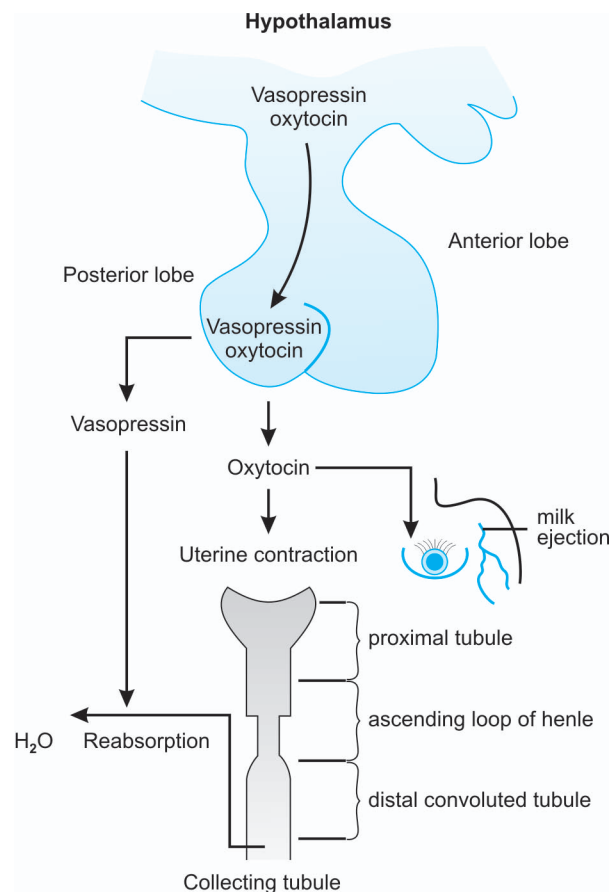


Fig. 8.1.6: Regulation and action of oxytocin and vasopressin

distal tubule and collecting ducts. V_{1a} receptors mediate contraction of vascular smooth muscle and V_{1b} receptors cause release of corticotropin from the anterior pituitary.

- Various preparations of vasopressin are available, which differ in route of administration, duration of action and relative selectivity for V_1 and V_2 receptors:

1. **V_2 receptor (selective) – Vasopressin** – short duration of action, given SC or IM. **Desmopressin** – longer acting, given as nasal spray. **Lypressin** – short acting, given as nasal spray.

2. **V_1 receptor (selective) – terlipressin** – longer acting, given IV **Felypressin** – short acting.

Disorder of ADH secretion results in diabetes insipidus, which can be **neurogenic** – due to reduced secretion of ADH or **nephrogenic** – due to impaired response of the nephron to ADH.

- Some drugs (lithium, demeclocycline, colchicine, vinca alkaloids) cause diabetes insipidus.

Clinical use of vasopressin and analogues

- Treatment of neurohypophyseal diabetes insipidus: lypressin, desmopressin.
- The initial treatment of bleeding esophageal varices: vasopressin, terlipressin, lypressin. (Octreotide is also used but sclerotherapy is the main treatment).
- As prophylactic therapy (e.g. **before tooth extraction**) in hemophilia: vasopressin, desmopressin (by increasing the concentration of factor VIII; somatostatin is also effective).
- Felypressin is used as a vasoconstrictor with local anesthetics
- Desmopressin is used in older children and adults with persistent enuresis.

Thyroid Hormones and Antithyroid Drugs

Thyroxine (T_4) and tri-iodothyronine (T_3) are the hormones secreted by the thyroid gland. T_4 is a less active precursor of T_3 .

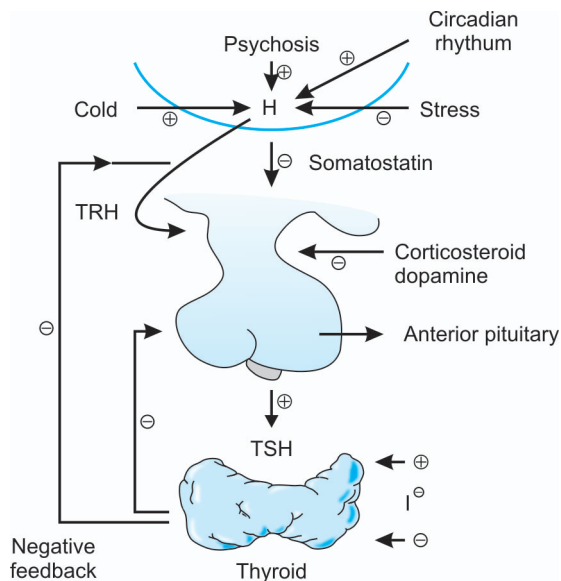


Fig. 8.2.1: Control of thyroid function (Hypothalamo-pituitary-thyroid axis)

Synthesis, storage and secretion (Fig. 8.2.1 and 8.2.2)

- Thyroid hormones are synthesized by iodination of tyrosine residues on thyroglobulin within the lumen of the thyroid follicle and are also stored in the thyroid follicles.
- The thyroglobulin is endocytosed and thyroxine (T_4) and triiodothyronine (T_3) are secreted.
- Synthesis and secretion of T_3 and T_4 are regulated by thyrotropin, and influenced by plasma iodide.
- The principle source of iodine is diet. Recommended iodine intake/day = 150 mcg/day (pool).

- The main steps involved in the synthesis of thyroid hormones are as follows: (See Fig. 8.2.3)

1. **Uptake:** of plasma iodide by thyroid cells by an active transport process. Thyroid glands take 75 mcg/day from the pool.
2. **Biosynthesis of Thyroid hormone**
 - **Oxidation** of iodide to I^+ (iodinium ions): by a peroxidase enzyme with the help of hydrogen peroxide.
 - **Iodination**: These combine with tyrosine residues of thyroglobulin (TG) to form moniodotyrosine (MIT) and diiodotyrosine (DIT).
3. **Coupling:** [pairing] of MIT and DIT. They are coupled to form T_3 and T_4 catalyzed by the same peroxidase enzyme.
 - $MIT + DIT = T_3$
 - $DIT + DIT = T_4$
4. **Storage**
 - TG containing iodinated tyrosine residues ($T_3 + T_4$) are stored in the follicles.
 - The hormones T_4 and T_3 are released into the circulation on requirement by proteolysis and exocytosis, and the secretion is regulated by **TSH** secreted by the anterior pituitary and **TRH** from the hypothalamus.
 - The secretion contains mixture of $T_3 + T_4 + MIT + DIT +$ Thyroglobulin and Tyrosin, where, $T_4:T_3 = 5:1$
5. **Transport and metabolism**
 - T_3 and T_4 reversibly bind with protein (TBG): Thyroid binding Globulin. During pregnancy TBG rises.
 - 0.04% of total T_4 and 0.4% total T_3 exist in free form.

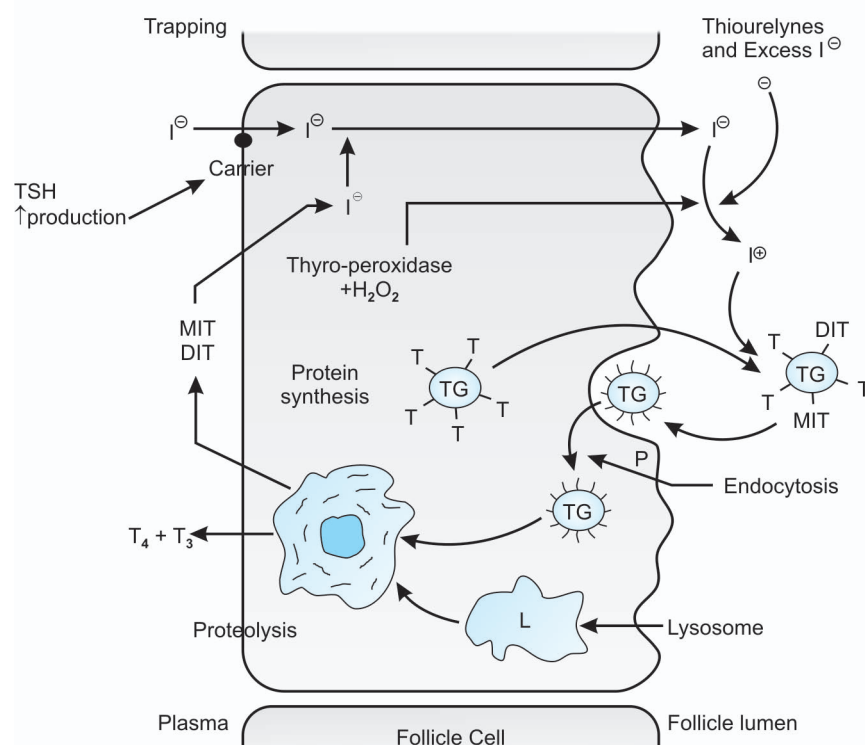


Fig. 8.2.2: Diagram of thyroid hormone synthesis and secretion

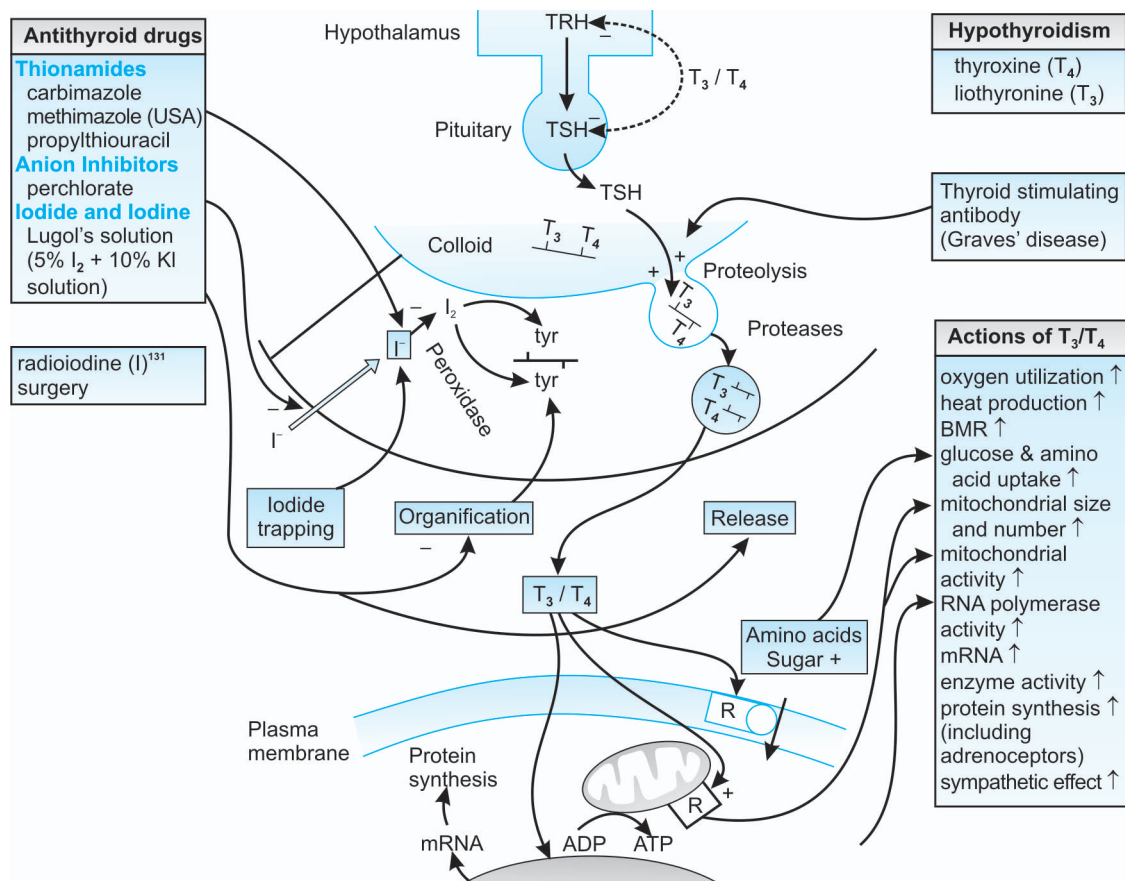
C = Carrier	P = Pseudopod
TG = Thyroglobulin	T = Tyrosine
MIT = Mono-iodotyrosine	DIT = Di-iodotyrosine
T_4 = Thyroxine	T_3 = Tri-iodothyronine
L = Lysosome	I^- = Iodide
THS = Thyroid stimulating hormone	

- Within cells, the T_4 is converted to T_3 (active) in liver and kidney, which interacts with a nuclear receptor, the receptor represses basal transcription when not bound to T_3 and activates transcription when bound. Both T_4 and T_3 are extensively bound to plasma proteins.
- The free hormone is metabolized in the liver and excreted in the bile.
- The $t_{1/2}$ of T_4 is 6-7 days and that of T_3 is 1-2 days. T_3 is 3-5 times more potent than T_4 and acts faster.
- There is a large pool of T_4 in the body; it has a low turnover rate and is found mainly intracellularly.

Pharmacological actions (Fig. 8.2.3)

T_3 and T_4 actions are:

- Stimulation of metabolism generally, causing increased O_2 consumption and increased metabolic rate. Thyroid hormones have important metabolic functions – they enhance carbohydrate and protein metabolism and stimulate lipolysis. They increase BMR.
- To influence growth and development. Thyroid hormones are essential for normal growth, development, function and maintenance of all body tissues.
- They facilitate erythropoiesis.
- They are essential for normal functioning of the CNS (mental retardation is seen in cretinism), skeletal muscles, cardiovascular system, reproductive system and gastrointestinal system.

Fig. 8.2.3: Synthesis, release and actions of T_3 and T_4 **Differences between T_3 and T_4**

T_3	T_4
- Fast onset of action (6-8 hours) - Effective in small doses - Four time more potent $T_{1/2} = 2$ days - Less tightly bound to plasma protein - Daily production – 30 μg - Serum levels $\left\{ \begin{array}{l} \text{Total} = 90-160 \text{ ng/dL} \\ \text{Free} = 0.2-0.5 \text{ ng/dL} \end{array} \right.$ - Fractional turnover/day – 60%	- Delayed onset of action (7-10 days) - Large doses are needed - Less potent $T_{1/2} = (6-7 \text{ days})$ - More tightly bound to plasma protein - Daily production - 80 μg - Serum level $\left\{ \begin{array}{l} \text{Total} = 5-12 \text{ mcg/dL} \\ \text{Free} = 0.7-1.8 \text{ ng/dL} \end{array} \right.$ - Fractional turnover/day – 10%

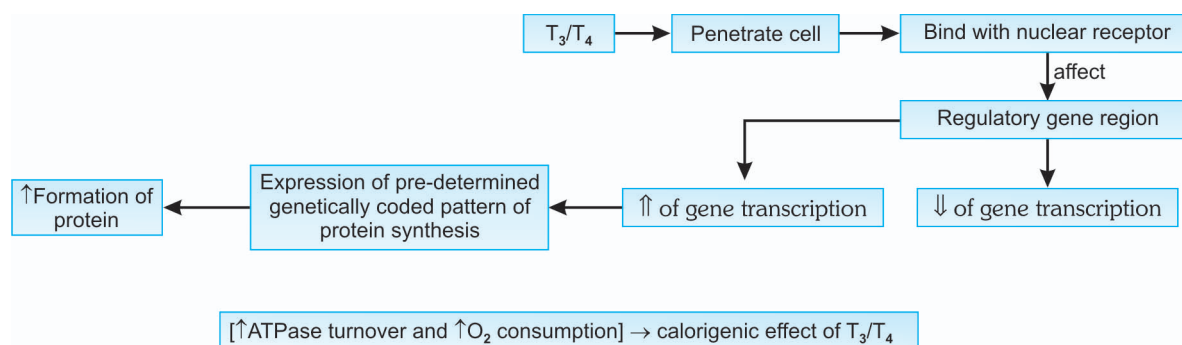


Fig. 8.2.4: Mechanism of action of T_3 and T_4

Site and mechanism of action (Fig. 8.2.4)

- Principally nuclear receptor.
- Membrane receptor.
- Mitochondrial receptor (increases oxygen consumption).

Abnormalities of thyroid include:

- **Hyperthyroidism** (thyrotoxicosis): *Excessive thyroxine secretion*: either diffuse toxic goiter or toxic nodular goiter

Clinical Features of Hyperthyroidism

- Flushed and warm skin
- Fast heart rate
- Palpitations
- Weight loss irrespective of increase in the appetite
- Anxiety with insomnia
- Diarrhea and Goiter.

- **Hypothyroidism**; *deficient thyroxine secretion*: in adults this causes **myxedema**, in infants this causes; **cretinism** and **simple non-toxic goiter**; due to dietary iodine deficiency, usually with normal thyroid function.

Clinical Features of Hypothyroidism

- Cold and dry skin
- Expressionless puffy face.
- Dry hair and scaly scalp.
- Thickened tissue, brittle nails.
- Abdominal distention, poor appetite and constipation.
- Bladder atony
- Husky and low pitched voice.
- Anemia with dilated heart.
- Menstrual irregularities in female

Therapeutic uses: Both thyroxine and tri-iodothyronine (liothyronine) are available and are given orally.

- **Replacement therapy:**
 - In *cretinism (child)*, treatment should be started immediately. Early treatment also prevent mental retardation. It should be continued life long.
 - *Hypothyroidism in adults* can be reversed by appropriate treatment.
 - *Myxoedema coma*, is a medical emergency. This condition is treated with IV thyroxine or liothyronine with prophylactic corticosteroids to avoid adrenal insufficiency.
- **Simple (non-toxic) goiter:** T_4 suppresses TSH production and the goiter regresses.
- **Papillary carcinoma of thyroid:** T_4 induces temporary remission.
- In the treatment of *chronic thyroiditis (hashimoto's disease)*.
- Hyperlipidemia associated with hypothyroidism.
- After I^{131} therapy: To treat post radiation hypothyroidism.
- **Miscellaneous:** Thyroxine is tried in refractory anemia, infertility, non-healing ulcers, obesity, delayed union of fractures, menopausal arthralgia, constipation, nephritic syndrome, etc.

Drug preparations for Hypothyroidism

- Thyroxine has all the actions of endogenous T_4 , given orally.
- Liothyronine – sodium (T_3) has all the actions of endogenous T_3 given intravenously.
- Thyroglobulin pigments, thyroid USP and Levothyroxine – sodium are the preparation which can be used for the treatment of hypothyroidism.

Hyperthyroidism and Antithyroid Drugs

- Hyperthyroidism is due to an excess of circulating thyroid hormones and could be due to various causes.

- ‘**Grave’s disease**’ an autoimmune disorder, is the most common cause. It is characterized by hyperthyroidism, diffuse goiter and IgG antibodies that activate TSH receptors.
- Hyperthyroidism secondary to anterior pituitary destruction: Simmond disease while chronic thyroiditis is hashimoto’s disease.
- Toxic nodular goiter:

Thyroid function test
1. Protein bound iodine (normal 2-8 mcg/dL) • Thyrotoxicosis: 10-12 mcg/dL • Myxedema: 2 mcg/dL
2. Serum T_4/T_3: measured by radioimmunoassay • T_4: 5-12 mcg/dL • T_3: 80-180 ng/dL
3. Serum TBG • Ratio of T_4 to TBG used as an index of free hormone activity
4. Free thyroxine index and effective T_4 ratio • Measured from serum T_4/serum TBG levels
5. Scintillography
6. T_3 suppression test (Radioactive iodine uptake) • In normal individual : RAIU is suppressed by 50% • In grave’s disease: NO suppression of RAIU

Classification of Antithyroid drugs

Drugs may act by inhibiting hormone synthesis

Antithyroid

- Propylthio-urecil (thiourea)
- Thio-imidazole: Carbimazole and methimazole

Drugs inhibit iodine trapping

- Thiocyanates (SCN)
- Perchlorates (ClO_4)
- Nitrates (NO_3)

Drugs inhibit hormone release

- Iodine
 - $Na^+ - K^+$ -Iodides and causes
 - Organic iodides / Lithium
- } **thyroid constipation**

Drugs destroying thyroid tissue

- Radioactive Iodine: I^{131} , I^{125} , I^{123} .

Others

- Drugs which inhibit conversion of T_4 to T_3 : **Amiodarone**.
- Drugs which inhibit iodination/coupling: **Sulfonamide and para-aminosalicylic acid (PAS)**

- Drugs causes metabolic degradation of T_3/T_4 :
 - Phenobarbitone
 - Phenytoin
 - Rifampicin
 - Carbamezapine

Few important drugs are described below:

Thionamides or Antithyroids or Thiourelines

- They reduce the synthesis of thyroid hormones by inhibiting iodination of tyrosine residues and coupling of iodotyrosine residues.
- **Propylthiouracil** also inhibits peripheral conversion of T_4 to T_3 . T_3 and T_4 levels fall. Large doses may stimulate release of TSH resulting in *thyroid enlargement*.
- **Carbimazole** is commonly used as it is more potent and long-acting. Adverse effects are *allergic reaction, jaundice, headache and rarely granulocytopenia*.

Therapeutic Uses

Hyperthyroidism

- a. *Grave’s disease or diffuse toxic goiter*: needs long-term (1-15 yrs) treatment with antithyroid drugs.
- b. *Toxic nodular goiter*: As an alternative—when surgery cannot be done as in the elderly.
- c. *Preoperatively*: hyperthyroid patients are made **euthyroidal** with antithyroid drugs and then operated.
- d. *Thyroid storm or thyrotoxic crisis* is sudden, severe exacerbation of thyrotoxicosis and can be life threatening. **Propylthiouracil, oral/rectal potassium iodide, IV hydrocortisone and supportive therapy are needed immediately.**

Thyroid storm: It occurs when the blood stream is suddenly flooded with thyroid hormones. It may occur after thyroid surgery or in untreated patients who suffer from infection or stress like trump, labor, or heart disease. It is characterized by hyper pyrexia and exaggeration of the pre-existing sign of thyrotoxicosis. It is treated with heavy doses of **propylthiouracil with iodide, beta blocker, IV fluids, antipyretic, and antimicrobials.**

Ionic Inhibitors (Drugs Inhibit Iodine Trapping)

- They interfere with the concentration of iodine by the thyroid gland.
- **Thiocyanate and perchlorate** inhibit the organification of iodine.

- Food like cabbage; cigarette smoking and sodium nitroprusside increase the concentration of thiocyanate in the blood.

Iodides (Drugs Inhibit Hormone Release)

- They inhibit the release of thyroid hormones and in thyrotoxic patients the symptoms subside in 1-2 days. The gland become firm, less vascular and shrinks in size over a period of 10-14 days.
- **Adverse effects** include *allergic reactions like skin rashes, conjunctivitis, swelling of the lips and salivary glands, fever and lymphadenopathy.*

Chronic overdose can cause *iodism with metallic taste, excessive salivation, lacrimation, running nose, sore throat, cough and rashes.*

- **Therapeutic uses**
 1. *Preoperative preparation for thyroidectomy:* Iodine is started just 10 days prior to surgery to make the thyroid gland firm and less vascular.
 2. *Thyroid storm:* Iodides act rapidly to reduce the release of thyroid hormones.
 3. *Prophylaxis:* Iodide is added to salt to prevent endemic goiter.
 4. *As an antiseptic*
 5. *Expectorant: Used in treatment of cough.*

Radioactive Iodine

Radioiodine is used:

- at first-line treatment for hyperthyroidism (particularly in the USA); recurrence is rare provided the dose is adequate
- for treatment of relapse of hyperthyroidism after thioureyne therapy or surgery.
- ^{131}I given orally as a solution, is rapidly absorbed and is concentrated by the thyroid in the follicles.
- It emits β rays which penetrate only 0.5 mm to 2 mm of the tissue so that it destroys only the thyroid tissue without damaging the surrounding structures.
- It is used in the treatment of hyperthyroidism and in thyroid carcinoma. *Small dose is also used for diagnostic purpose in thyroid function tests.*

β -adrenergic blockers

- Many of the symptoms of hyperthyroidism are of sympathetic overactivity as there is increased tissue sensitivity to catecholamines in hyperthyroidism.
- β -adrenergic blockers like **propranolol** relieve symptoms like *palpitation, tremors, nervousness, sweating and myopathy.*
- They only afford symptomatic relief and are used as adjuvant.

Pharmacotherapy for Thyrotoxic goiter

1. Correction of sympathetic over activity

- Beta blocker (propranolol): 40 mg, 6 hourly orally/ 2 mg - 6 hourly IV.
- Reserpine : 2.5 mg IM 6 hourly

2. Correction of adrenal insufficiency:

- Hydrocortisone: 200 mg

3. Blockade of further thyroid hormone synthesis:

- Sodium Iodide: 1–2 gm (slow IV).
- Oral antithyroid: Neomercazole 100 mg loading dose followed by 15 mg tid.

4. Heart failure require: Digitalization and diuretic therapy.

5. General measures:

- Sponging (for hyperpyrexia)
- Oxygen therapy
- IV – Glucose.

6. Plasmapheresis

Calcitonin: It is secreted from para follicular C cells of thyroid. The secretion is regulated by concentration of calcium in the plasma. Higher is the concentration of calcium, more is the secretion of calcitonin. It inhibits bone resorption and thereby reduces blood level of calcium and phosphorus. Therapeutically it is indicated in hyperparathyroidism, to inhibit bone remodeling, vitamin D intoxication, idiopathic hypercalcaemia in Infant, paget's disease, etc.

Agents Affecting Bone-Mineral Turnover

Bone Metabolism

- Calcium and phosphorus are the important minerals of the bone with approximately 1-2 kg of calcium and 1 kg of phosphorus stored in it.
- Calcium and phosphorus metabolism are primarily regulated by **vitamin D** and parathyroid hormone: **parathormone**.
- Other hormones that also influence calcium and phosphorus metabolism are **calcitonin, growth hormone, insulin, thyroid hormone, prolactin, glucocorticoids and sex hormones**.

CALCIUM

Physiological role of Ca^{++} in the body

- After C, H, O, N, Ca^{++} is the most abundant in body (2% of body weight).
- Calcium is essential for tissue excitability, muscular excitation-contraction coupling, secretion from glands, myocardial contractility and formation of bone and teeth.
- It also maintains the integrity of mucous membranes and cell membrane.
- Calcium is essential for normal blood coagulation.

Bone structure and composition

- Human skeletal has 80% cortical bone (shaft of the bone), while 20% trabecular bone (epiphysis of long bones, ribs, pelvis, etc.)
- Ca^{++} and phosphorus are the main mineral constituents in the bones.

- The organic matrix of the bone is called – *Osteoid* [*Collagen + Osteocalcin + Phosphoprotein*].
- Osteocalcin is : Vit. K dependent protein, while phosphoprotein is also called as osteonectin.
- The Osteoid of the bone is mineralized by calcium phosphate crystals in the form of hydroxyapatite.

Bone Remodeling

- Osteoclast activity : [Bone resorption]
- Osteoblast activity : [Bone formation]
- Other factors involved in bone remodeling are :
 - a. Ca^{++}
 - b. Phosphate
 - c. Cytokines (IL – 6) and IGF – 1 (Insulin like growth factor)
 - d. Hormones like : PTH, Calcitonin, Vitamin D
 - e. Diet, Drugs, Physical exercise, etc.

Ca^{++} Metabolism (Fig. 8.3.1)

- The normal plasma calcium level is 9-11 mg/dL.
- 40% bind with plasma protein, 10% complexed with citrate or phosphate while 50% is present in ionized form.
- Calcium is absorbed from the small intestine by a carrier mediated active transport.
- Normally about 30% of the dietary calcium is absorbed, while in Ca^{++} deficiency, the absorption increases under the control of vitamin D .
- It is excreted in feces, urine and sweat.

PTH		Vitamin D
Intestine	Increase in Ca^{++} and PO_4 reabsorption	Increase in Ca^{++} and PO_4 reabsorption
Kidney	Decrease Ca^{++} excretion Increase PO_4 excretion	Decreases Ca^{++} and PO_4 excretion
Bone	Increase resorption of both	Increase resorption of both

Contd...

Contd...

PTH	Vitamin D
Net effect Increase in Serum Ca^{++} Decrease in Serum PO_4 $\uparrow$ osteoclastic activity.	Increase in both serum Ca^{++} and PO_4 $\uparrow$ osteoclastic activity.

Some preparations of calcium

Salt	Formulation	Dose
Calcium gluconate	10% inj – given IV 500 mg, 1 g tablets	10-20 ml
Calcium chloride	5-10% solution IV	5-10 ml

- Hypocalcemia leads to Tetany other preparations like calcium lactate, ca-dibasic phosphate and calcium carbonate can also be used.

- IV calcium is used in weakness, pruritus and some dermatitis. The feeling of warmth produced by the injection could afford psychological benefit.

Adverse effects: Oral calcium can produce constipation, bloating and abdominal bulge, etc.

Disorders of Bones

- Osteomalacia:** Soft bone due to defect in bone mineralization
- Rickets:** Soft bone (bow like legs in children)
- Osteopenia:** Decrease in mineral content
- Osteoporosis:** Postmenopausal reduction in bone mass

PHOSPHATE

- Phosphates play a significant role in various enzymatic reactions, which are important for the structure and function of the cells and are important constituents of **teeth and bone**.
- Phosphorus is absorbed by the small intestine and excreted through kidneys under the influence of parathyroid hormone: *parathormone*.
- Hypophosphatemia is responsible for muscle weakness and abnormal bone mineralization.

PARATHYROID HORMONE (PARATHORMONE, PTH) (Fig. 8.3.1)

- Parathormone is a peptide secreted by the parathyroid gland.
- PTH is a single peptide chain of 84 amino acids that regulates the concentration of Ca^{2+} and phosphate levels in the extracellular fluid.

Physiological role of parathyroid hormone (PTH, parathormone):

- Secretion of PTH is regulated by plasma Ca^{++} concentration – low plasma Ca^{++} stimulates PTH release, while high levels inhibit secretion.

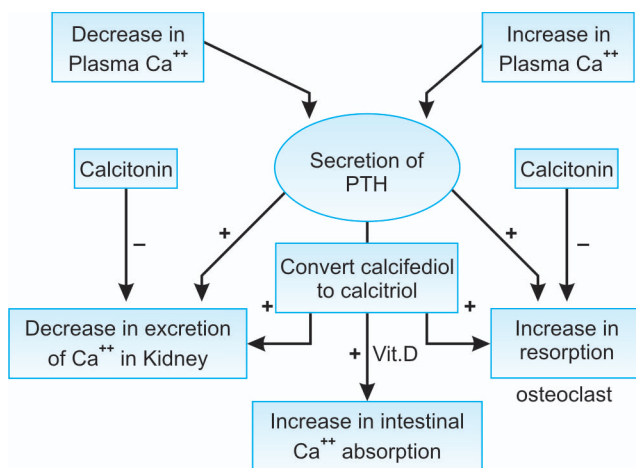


Fig. 8.3.1: Regulation of plasma Ca^{++} level

Uses

- To prevent and treat calcium deficiency.**
 - Calcium supplements are given orally in children, pregnant and lactating women and in postmenopausal **osteoporosis** to prevent calcium deficiency.
 - Tetany:** 5-10 ml IV calcium gluconate followed by 50-100 ml slow IV infusion promptly reverses the muscular spasm. The injection produces a sense of warmth. This is followed by oral calcium 1.5 g daily for several weeks.
 - Vitamin D deficiency rickets - calcium is given along with vitamin D.
- Calcium carbonate is used as an antacid.

- PTH acts on various peripheral tissues to mobilize Ca^{2+} into the extracellular fluid and restore the concentration to normal when it has been lowered.
 1. PTH increases the active absorption of Ca^{2+} from the small intestine. This is a vitamin D-dependent process.
 2. PTH increases the rate of bone resorption of Ca^{2+} and phosphate.
 3. At physiological doses, PTH increases the renal tubular reabsorption of Ca^{2+} and the excretion of phosphate. The effects on both bone and kidney are probably mediated via cAMP.

Pharmacokinetics: PTH has a plasma half-life of about 2-5 minutes and is rapidly removed by the liver and kidney.

Diseases of the Parathyroid gland:

Hypoparathyroidism is one of many causes of hypocalcemia.

Symptoms and signs

- Paresthesias of the extremities, tetany, laryngospasm, and eventually generalized convulsions. Spasms of smooth muscle can also occur.
- Electrocardiographic changes can include marked tachycardia.

Treatment

- Dietary supplementation of vitamin D and Ca^{2+} is the principal form of treatment.

Hyperparathyroidism

Etiology

- The primary form of hyperparathyroidism is due to parathyroid hyperplasia or adenoma or due to tumors at other sites.
- The secondary form is a result of conditions producing a negative Ca^{++} balance, such as malabsorption or renal disease.

Symptoms and signs

- Hypercalciuria (which can result in a renal calculi), muscle weakness, constipation, nausea, and vomiting.

Treatment

- Usually by surgical resection, although long-term therapy with neutral phosphate, a low-calcium diet, and fluids may be given to those patients who are poor surgical candidates.

CALCITONIN (Fig. 8.3.1)

General considerations

- Calcitonin is a peptide hormone secreted by the parafollicular 'C' cells of the thyroid gland. Parafollicular

C cells are also found in the parathyroid and thymus. Parafollicular C cells of the thyroid are the site of production and secretion of **calcitonin**.

- The synthesis and secretion of calcitonin are regulated by the plasma Ca^{2+} concentration. cAMP, epinephrine, glucagon, gastrin, and cholecystokinin all stimulate calcitonin release after ingestion of Ca^{2+} salts.
- By altering osteoclastic and osteocytic activity, calcitonin can directly inhibit bone resorption. ($\uparrow$ osteoblastic activity)
- Calcitonin, in part by a cAMP-mediated reaction, increases kidney excretion of Ca^{2+} , phosphate, and sodium (Na^+).

Therapeutic uses: The major uses of calcitonin are to decrease hypercalcemia and hyperphosphatemia in patients with:

- Hyperparathyroidism
- Idiopathic hypercalcemia of pregnancy
- Vitamin D intoxication
- Osteolytic bone metastases
- Calcitonin may decrease the rate of bone loss in patients with postmenopausal osteoporosis.
- Although, calcitonin is effective for the treatment of Paget's disease of bone, patients may become resistant to therapy within several months.

Preparations and route of administration

- Salmon and human calcitonin are used clinically.
- They are administered subcutaneously or intramuscularly. A nasal formulation is also under development.

Adverse effect includes: Occasional edema, nausea and the stimulation of neutralizing antibody formation.

BISPHOSPHONATES (PAMIDRONATE, ALENDRONATE)

Sodium etidronate

- Mechanism of action:** Sodium etidronate is thought to slow the formation and dissolution of hydroxyapatite crystals.
- Pharmacologic effects:** Its advantages over calcitonin include oral efficacy and lack of antigenicity.
- Therapeutic uses:** Sodium etidronate is used in the treatment of Paget's disease of bone, hypercalcemia and is tried in postmenopausal osteoporosis.
- Route of administration:** Etidronate disodium is given orally. Daily doses, given for not more than 6 months, may produce a long-lasting remission.
- Adverse effects:** Fever, gastritis and hypocalcemia can occur. Long-term use can lead to osteomalacia due to inhibition of bone mineralization.

Other hormones that regulate bone turnover

They are glucocorticoids and estrogens.

- **Glucocorticoids:** They antagonize vitamin D stimulated intestinal calcium absorption and enhance renal Ca^{++} excretion. They are essential for osteoblast differentiation. They are antagonists of VD.
- **Estrogen:** Estrogen receptors are found in bone which suggests that they may also have a direct effect on bone remodeling. They inhibit cytokines (which recruit osteoclast) therefore oppose bone resorption. Therefore osteoporosis in postmenopausal condition is treated with HRT (estrogen)
- **Antiestrogens: Tamoxifen/Raloxifen.** They have antiestrogenic action on mammary glands while they have estrogenic action on bone.

VITAMIN D

- Vitamin D (prehormone) a fat-soluble vitamin, is produced in the skin from 7-dehydrocholesterol in presence of ultraviolet rays.
- It is converted to active metabolites in the body which regulate plasma calcium levels and various function of the cells.

Source

- Diet as ergocalciferol (vitamin D_2) from plants.
- Cholecalciferol (vitamin D_3) is synthesized in the skin from 7-dehydrocholesterol.
- Cholecalciferol (Vitamin D_3) is converted to 25-OHD₃ (calcifediol) in the liver which is in turn converted to 1,25-dihydroxycholecalciferol (calcitriol) in the kidney.
- Calcitriol is the active form of vit D while calcitriol is the main metabolite in circulation.
- Conversion of calcifediol to calcitriol is influenced by PTH and plasma phosphate concentration.

Actions

The chief actions of calcitriol are:

- mobilizes calcium from bone by promoting osteoclastic activity.
- it stimulates calcium and phosphate absorption in the intestine.
- increases reabsorption of Ca^{++} from kidney tubules.
- *Calcitriol is essential for normal bone mineralization. It is essential for skeletal muscles as well as cellular growth and differentiation.*

- Vitamin D deficiency results in low plasma calcium and phosphate levels with abnormal mineralization of the bone; causes rickets in children and osteomalacia in adults.

Pharmacokinetics

- Given orally, vit D is well-absorbed from the small intestines in the presence of bile salts.
- It is converted to 25-(OH) D_3 in the liver and circulates in the plasma, bound to a protein and is stored in the adipose tissue.
- Vitamin D is also degraded in the liver and the metabolites are excreted in the bile.
- Daily requirement – 400 IU (10 mg).

Preparations

- Calciferol capsules 25,000; 50,000 IU.
- Cholecalciferol granules – oral 60,000 IU in IG; 3,00,000 IU/ml; 6,00,000 IU/ml inj.
- Shark liver oil with vit D – 1000 IU/ml, vit A – 6000 IU/ml.

Adverse effects

- High doses of vitamin D used for long periods result in hypervitaminosis D manifesting as generalized decalcification of the bones, hypercalcemia, hyperphosphataemia resulting in weakness, drowsiness, nausea, abdominal pain, thirst, renal stones and hypertension.
- Hypervitaminosis D in children is most often due to unnecessary vitamin D supplementation by parents.

Therapeutic Indications

- **Hypoparathyroidism:** Calcitriol with Ca^{++} supplements are beneficial.
- **Nutritional rickets and osteomalacia:** 6,00,000 units IM repeated after 4-6 weeks is needed in rickets and osteomalacia along with calcium supplements.
- **Vitamin D dependent rickets** is due to calcitriol deficiency and is treated with calcitriol.
- **Vitamin D resistant rickets** is a hereditary disorder with abnormality in renal phosphate reabsorption. Phosphate with vitamin D is found to be useful.
- **Senile osteoporosis:** Oral vitamin D supplements with calcium may be tried.
- **Prophylaxis:** 400 IU daily or 3,00,000 IU every 3-6 month IM prevents vitamin D deficiency. In the breastfed infants, from the first month onwards oral vitamin D supplements are needed. In obstructive jaundice, prophylactic 6,00,000 units vit D given IM prevents deficiency.

Diabetes Mellitus, Insulin and Oral Hypoglycemic Agents

Definition: Diabetes mellitus is a chronic metabolic disorder characterized by:

- Hyperglycemia and altered metabolism of carbohydrates, lipids and proteins.
- It is also characterized by: **polyphagia, polyurea and polydypsia.**
- It is a common condition affecting 1-2% of population with a strong hereditary tendency.

Diabetes mellitus can be of 2 types.

Type I: Insulin dependent diabetes mellitus (IDDM)

- It is an autoimmune disorder where antibodies destroy the β cells of the islets of langerhans. There is complete failure of pancreatic beta cell function. By contrast, alpha islet cells secreting glucagon, delta cells secreting somatostatin, and pancreatic polypeptide cells are preserved,
- It usually occurs in the young children and adolescents (hence called juvenile onset diabetes mellitus).
- In this type I diabetes, there is no circulating insulin in the plasma and, thus, insulin replacement is required.
- The patient is prone to both hyperglycemia and ketoacidosis, which occur late in the course of the disease after most beta cells are destroyed.

Type II: Non-insulin dependent diabetes mellitus (NIDDM)

- It is of maturity onset. Most patients are obese.
- There is both reduced sensitivity of tissues to insulin and impaired regulation of insulin secretion.
- Type II diabetes may be due to a defect in the receptor on the pancreatic beta cell membrane.
- In the earliest forms of the disease, there is a delay in the initial secretion of insulin after stimulation by glucose.
- The patient is not prone to ketoacidosis.

- Also, less insulin than normal is secreted at any given glucose concentration.

In both types of diabetes mellitus, plasma immunoreactive glucagon concentrations are increased, especially during ketoacidosis. The normal suppression of glucagon by hyperglycemia is also impaired.

The pathognomonic finding of capillary basement membrane thickening occurs early in the course of diabetes mellitus. It is this change that is probably responsible for the major complications of diabetes, including:

1. Microangiopathy
2. Nephropathy
3. Neuropathy
4. Retinopathy
5. Atherosclerosis: This disorder occurs more often in diabetics than in nondiabetics.

INSULIN: In 1921, Banting and Best first extracted insulin from the pancreas. In 1922 insulin was first used on a 14 years old boy, suffering from severe diabetes mellitus with excellent response. Insulin was then purified in few years (Fig. 8.4.1).

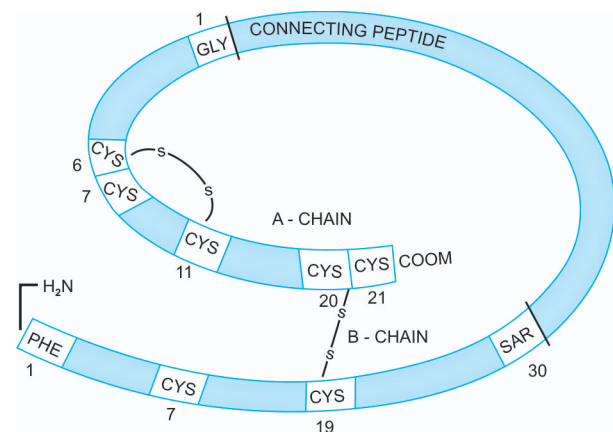


Fig. 8.4.1: Structure of insulin

Chemistry, Synthesis and Secretion

Chemistry of insulin

- Insulin consists of two amino acid chains joined together by disulfide linkages; it has a molecular weight of about 6000.
- Pancreatic beta cells form insulin from a single-chain precursor, pre and proinsulin → proinsulin, which possesses little biologic activity.
- Insulin can exist as a monomer, a dimer, or a hexamer consisting of three dimers.
 - a. Two molecules of zinc are coordinated in the hexamer form, and it is this form that is stored in the granules of the beta cell.
 - b. The biologically active form is thought to be the monomer.
- There are species variations in the amino acid sequence of insulin.
- Human insulin differs from bovine insulin by 3 amino acids and from porcine insulin by 1 amino acid. It is stored in granules in the β islet cells of pancreas. Hence, porcine insulin is closer to human insulin.

Pharmacokinetics

Regulation of Insulin secretion (Fig. 8.4.2)

- Normal pancreas releases about 50 units of insulin everyday. The secretion is regulated by factors like food, hormones and autonomic nervous system. Blood glucose concentration is the main factor.
- The islet of Langerhans are composed of 4 types of cells – β cells secrete insulin, α (A) cells glucagon, δ (D) cells somatostatin and P cells secrete pancreatic polypeptide.

Stimuli for insulin secretion

Chemical regulation

- Oral glucose has a greater ability to stimulate insulin secretion than intravenously administered glucose. Fatty acids, amino acids, and ketone bodies all increase insulin secretion. Glucose-induced insulin release appears to occur in two phases:
 - a. An initial-burst phase, which peaks in minutes and then rapidly declines.
 - b. A slow phase, which takes an hour to reach a peak.

Hormonal regulation

- Gastrointestinal hormones, such as secretin, pancreatico-zymin, and gastrin, can stimulate insulin secretion.

Neuronal regulation

- Primary center for regulation: Hypothalamus ventrolateral nuclei : Stimulate insulin release, while ventromedial nuclei inhibit insulin release.

- Autonomic control of insulin secretion
 1. β -adrenergic agonists increase insulin secretion by increasing intracellular cAMP.
 2. cAMP plus Ca^{++} may activate a microtubular-microfilament system that promotes the release of the insulin granule.
 3. Cholinergic activation (Ach) : It increases insulin secretion through IP_3/DAG mediated increase in intracellular $[\text{Ca}^{++}]$.
 4. Adrenaline (α_2) agonist inhibit insulin release.
- Most secreted insulin circulates in the blood and lymphatic system as the free hormone.
- Although small quantities of insulin can be detected in the urine, the kidney normally filters and reabsorbs the hormone.
- Both the liver and the kidney are of primary importance in the degradation of insulin by a proteolytic enzyme. Each is capable of destroying 40% of the insulin produced per day.

Action of Insulin (Fig. 8.4.2)

1. Carbohydrate metabolism

- Insulin stimulates the uptake and metabolism of glucose in the peripheral tissues especially skeletal muscles and fat.
- It inhibits glucose production in the liver by inhibiting gluconeogenesis and glycogenolysis. By the above actions, insulin lowers the blood glucose concentration.
- It stimulates glycogenesis in liver, muscle and fat tissues.

2. Lipid metabolism

- Insulin inhibits lipolysis in adipose tissue and promotes the synthesis of triglycerides. In diabetes, large amounts of fat are broken down. The free fatty acids so formed are converted by the liver to acetyl CoA and then ketone bodies. This results in ketonemia and ketonuria.

Note: Glucose entry in liver, brain, RBCs, WBCs and renal medullary cells is largely independent of insulin.

- Insulin indirectly enhances lipoprotein lipase activity resulting in increased clearance of VLDL and chylomicrons. In insulin deficiency, there is hypertriglyceridemia.

3. Protein metabolism

- Insulin facilitates amino acid uptake and protein synthesis and inhibits protein break down anabolic effect.
- In diabetes, there is increased catabolic effect and negative nitrogen balance.

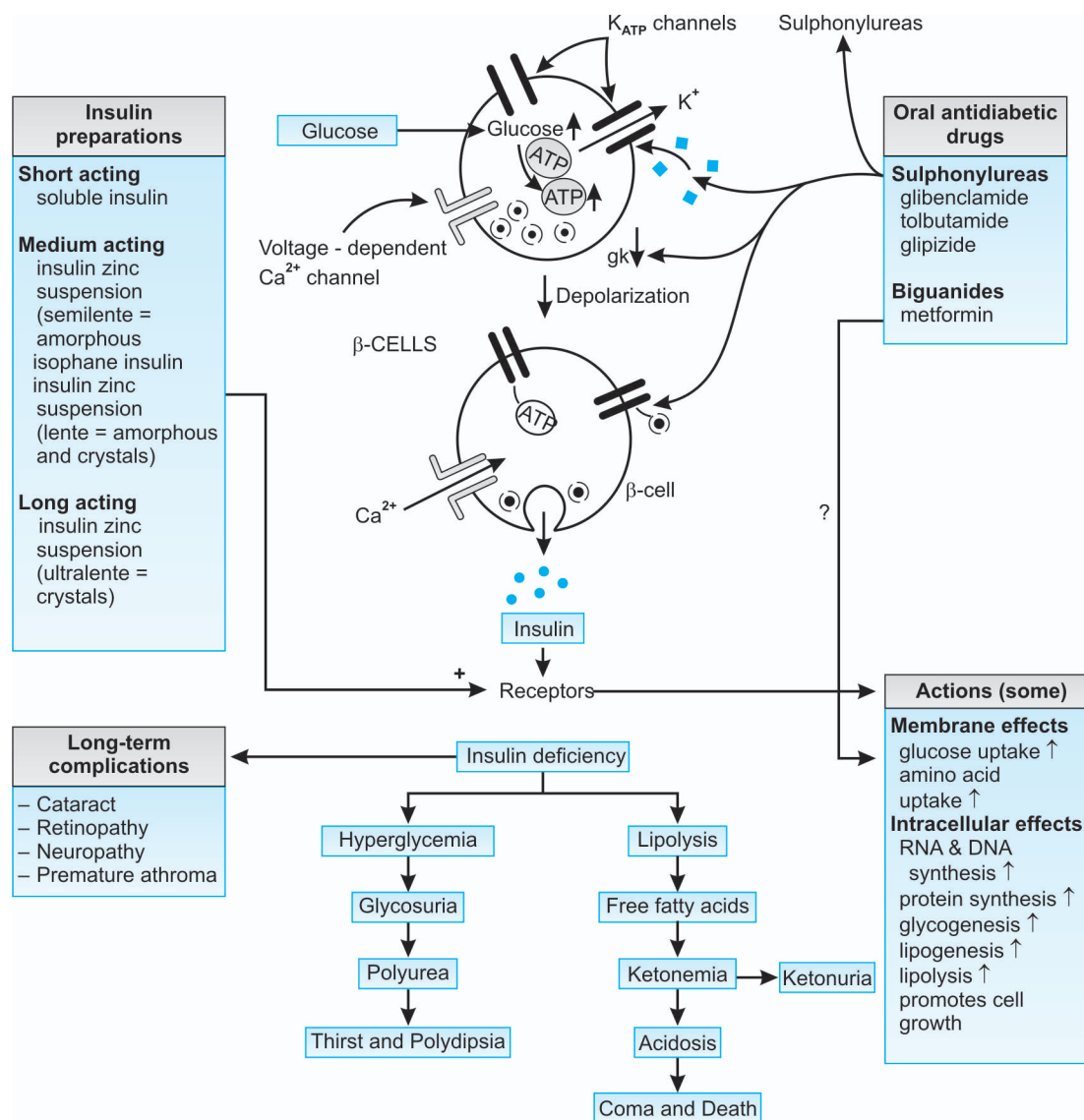


Fig. 8.4.2: Insulin release, action of insulin and oral antidiabetic drugs

Mechanism of action: Insulin binds to specific receptors present on the surface of target cells and stimulates tyrosine kinase activity. This in turn activates a cascade of phosphorylation and dephosphorylation reactions which stimulate or inhibit the enzymes involved in the metabolic actions of insulin.

Metabolic Effects of Insulin Deficiency

- Reduced rate of glucose transport:** When insulin is deficient, there is a reduction in the rate of transport of glucose across the membranes of certain cells, including muscle and adipose cells. Insulin does not significantly influence the rate of glucose transport across liver

cells, erythrocytes or leukocytes, and the rate of entry of glucose into the brain is only affected in ketoacidosis.

- Reduced enzyme activity:** There is a reduction in the activity of the enzyme systems necessary for catalyzing glucose to glycogen.
- Hyperlipemia, ketonemia, and acidosis** can all occur with insulin deficiency. The lack of insulin allows hormone-sensitive lipase to mobilize fatty acids, which leads to elevated circulating levels of ketones, acetoacetate, and β -hydroxybutyrate.
- Azoturia:** Insulin deficiency combined with glucagon excess results in the conversion of large amounts of protein to glucose, resulting in an increased excretion of urea and ammonia.

INDICATIONS OF INSULIN

1. In all cases of Type 1 diabetes mellitus.
2. In the following cases of Type II DM where
 - a. Diet/Exercise/Oral-Hypoglycemic drug fails.
 - b. Oral hypoglycemic drugs are contraindicated.
 - c. Emergency like: **Diabetic ketoacidosis**
 - d. Pregnancy, injury, stress or surgical procedure is required.

Side effects

1. **Hypoglycemia** is the most common complication of insulin therapy. It may be due to too large dose, inappropriate time of administration, unusually small meal or vigorous exercise. Symptoms – sweating, palpitation, tremors, blurred vision, weakness, hunger and confusion. Severe hypoglycemia may result in convulsion and coma.

Treatment: Oral glucose or fruit juice like orange juice or in severe cases IV glucose promptly reverse the symptoms.

2. **Lipodystrophy:** Atrophy of the subcutaneous fat at the site of injection may be due to immuneresponse to contaminating proteins. It is rare with purified preparations. Insulin absorption may be irregular and can be prevented by using different sites for injection.
3. **Allergy:** This is due to the contaminating proteins. Urticaria, angioedema and rarely anaphylaxis can occur. It is rare with purified preparations and human insulin.
4. **Edema:** Some severe diabetics develop edema which is self-limiting.

Preparations of Insulin: The types of insulin differ in their onset and duration of action. The potency of insulin is expressed in USP units. They are of following types:

Crystalline zinc insulin (regular insulin)

- Regular insulin is a short-acting, soluble insulin, which is prepared in a phosphate buffer with zinc at a pH of 3.5.
- Its peak action occurs in 2-4 hours and its duration is 5-7 hours.
- It can be administered subcutaneously or intravenously and is a good agent for controlling diabetic ketoacidosis rapidly.
- The frequency of injections (4-5/days) is not very convenient.

Protamine zinc insulin

- Adding the basic protein protamine to crystalline zinc insulin causes the formation of large crystals. This produces a compound that is less soluble.

- When injected, this formulation serves as a tissue depot, producing slow absorption into the bloodstream.
- The action of protamine zinc insulin peaks in 16-18 hours and lasts up to 36 hours.
- Fine control of hyperglycemia is difficult with such a long-acting preparation.

Isophane insulins [Neutral Protamine Hagedorn (NPH)]

- This intermediate-acting insulin is similar to protamine zinc insulin, but it contains only a small amount of protamine (0.5 mg/100 units of insulin). Therefore, NPH insulin has an earlier onset and earlier peak effects than protamine zinc insulin, but the duration of action is similar for both preparations.
- The effects of NPH insulin peak in 8-12 hours and have a duration of 24-48 hours.
- These effects are clinically equivalent to combining 2-3 units of crystalline zinc insulin with 1 unit of protamine zinc insulin.

Lente insulins

- Lente insulins do not contain protamine; their insolubility results from the addition of excess zinc in an acetate rather than a phosphate buffer.
- The onset of action for the lente insulins depends on the physical state, the ambient zinc concentration, and the pH.
 1. A microamorphous crystalline form, known as *prompt insulin zinc suspension* (semilente insulin), peaks in 4-8 hours and has a duration of action of 12-16 hours.
 2. A large crystalline form with a high zinc content, known as *extended insulin zinc suspension* (ultralente insulin), has an onset and duration of action similar to those of protamine zinc insulin.
 3. Combining 7 parts of ultralente with 3 parts of semilente produces insulin zinc suspension (lente insulin), which is similar to NPH insulin in its onset and duration of action.

Human insulins

- Human insulins are produced by semisynthetic and recombinant DNA techniques.
- Since the human proinsulin gene was synthesized, human proinsulin has been produced on a large scale as the precursor to human insulin.
- The biologic activity and intravenous pharmacokinetics of human insulin are similar to porcine insulin. It is absorbed more quickly than porcine insulin after subcutaneous injection, thereby improving glycemic control after meals.
- Human insulins are useful for individuals with an allergy to insulin from animal sources.

Insulin Resistance

Definition: If insulin requirement is increased then normal, i.e.

- Conventionally > 200 U/day
- Physiologically > 100 U/day

1. Acute insulin resistance : It is develop because of acute infection, trauma, surgery, stress, ketoacidosis, etc.

Treatment: ↑ doses of regular insulin.

- removal of the cause.
- It will disappear's later on

2. Chronic insulin resistance : It is specifically seen in such patients who are treated with conventional beef or pork insulin for long time.

Treatment: Switching over to the more purified newer preparations. (discussed later)

Insulin Analogus: Lispro insulin

* Lysine B²⁸ + Proline B²⁹ = Lispro

- Rapid absorption
- Act within 15 minute after subcutaneous injection
- Peak 60-90 minutes.
- Duration of action 4-5 hours.

Preparations of Insulin

Preparation	Onset	Duration
SHORT-ACTING	(hr)	(hr)
Regular (Plain, soluble)	0.5-1	8
Semilente (Insulin zine suspension/amorphous)	1	14
INTERMEDIATE-ACTING		
Lente (Insulin zine suspension)	2	24
NPH (Neutral protamine hagedorn) or Isophane insulin	2	24
LONG-ACTING		
Ultra lente(Insulin zine suspension crystalline)	6	36
PZI (protamine zine insulin)	6	36
Lispro: ultra short acting insulin		

Disadvantages of the conventional preparations are that:

- I. They are allergic because of the impurities (1%) and their animal source.
- II. They are not very stable.

Hence, highly purified preparations are now made available which are having advantages of being less antigenic, more stable, less resistance and lipodystrophy. But they are all expensive.

Highly Purified Insulins

1. *Single peak insulins:*

- Actrapid – highly purified porcine regular insulin
- Lentard – highly purified porcine lente insulin

2. *Monotard (MC) Insulins:* Actrapid MC – Monocomponent porcine regular insulin.

- Monotard MC – Monocomponent porcine lente insulin.

Indications for highly purified/human insulins

1. Allergy to conventional preparations.
2. Insulin resistance.
3. Lipodystrophy at the site of injection.
4. Pregnancy/emergency.
 - Insulin analogs with favorable pharmacokinetic properties have been synthesized. Insulin lispro is an analog which is absorbed much faster.
 - Glargine is a long-acting analog which acts for 24 hr. The effects is peakless but attains a broad plasma concentration plateau.

Route of Administration

- The usual route of administration for all insulin preparations is subcutaneous. The limitation of this route is the variability of insulin absorption from the depot injection site.
- Insulin is administered intravenously during emergency circumstances. If administration is via this route, the crystalline form is used. Recently, peritoneal infusion and intranasal administration with adjuvants have resulted in successful hormone replacement therapy.
- Intensified treatment regimens, including multiple daily injections and continuous subcutaneous infusion have been used to mimic the physiological replacement of insulin.
- Insulin is a protein and cannot be given orally because it would be digested.
- Insulin delivery devices have been designed which make insulin administration more convenient.
- Portable pen injectors are small pen-size devices containing multiple doses of insulin and retractable needles. They can be carried while traveling and to the place of work.
- Insulin pumps deliver appropriate doses of insulin on the basis of self-monitored blood glucose results. The set is inserted subcutaneously.
- Alternate routes of insulin delivery have been tried—inhaled insulin and insulin nasal spray are being evaluated for use. Clinical trials are also going on for oral insulin. (i.e. special preparation).

Drug interactions

1. β -adrenergic blockers mask tachycardia, the important warning symptom of hypoglycemia. They also prolong hypoglycemia by inhibiting compensatory mechanisms acting through β_2 -receptors.
2. Salicylates precipitate hypoglycemia by enhancing insulin secretion and β cell sensitivity to glucose.

Oral hypoglycemic drugs: The main disadvantage of insulin is the need for injection. The advent of oral hypoglycaemics came as a boon to millions of NIDDM patients with early and mild diabetes. Sulfonylureas were the first oral antidiabetics (OAD) to be made available in 1950s. We now have 4 groups of oral hypoglycemics—sulfonylureas, biguanides, alpha glucosidases Inhibitors (e.g. acarbose) and thiazolidinediones, (e.g. pioglitazone and rosiglitazone).

Classification**1. Sulfonylureas**

Ist Generation: Tolbutamide, Chlorpropamide, Acetohexamide, Tolazamine.

IInd Generation: Glibenclamide, Glipizide, Gliclazide.

2. Biguanides: Phenformin, Metformin.**3. Miscellaneous:** Acarbose, pioglitazone, rosiglitazone.

Sulfonylureas: A sulfonamide derivative used for its antibacterial effects in typhoid patients produced hypoglycemia. This observation led to the development of Sulfonylureas.

Mechanism of action (Fig. 8.4.2)

They reduce the blood glucose level by:

1. Stimulating the release of insulin from the pancreatic β cells.
2. Increasing the sensitivity of peripheral tissues to insulin.
3. Increasing the number of insulin receptors.
4. Suppressing hepatic gluconeogenesis.
 - Sulfonylureas bind to receptors on pancreatic β cells, cause depolarization and Ca^{++} influx leading to increased insulin secretion. Thus some functional β cells are essential for their action.

Pharmacokinetics

- Sulfonylureas are well-absorbed orally,
- They are extensively bound to plasma proteins,
- They are metabolized in the liver and some are excreted in the urine. Hence, they should be avoided in patients with renal or liver dysfunction.

Adverse effects

- Second-generation agents having fewer adverse effects.
- Hypoglycemia is the most common adverse effect, least with tolbutamide due to short $t_{1/2}$ and low potency.
- Nausea, vomiting, jaundice, and allergic reactions can occur. Patients on sulfonylureas may have an increase

in the rate of cardiovascular death. However, this is still controversial and sulfonylureas continue to be used.

Drug interactions

Drugs that augment hypoglycemic effect:

- NSAIDs, warfarin, sulfonamides – displace sulfonylureas from protein binding sites.
- Alcohol, chloramphenicol, cimetidine – inhibit metabolism

Drugs that decrease the action of sulfonylureas:

- Diuretics and corticosteroids – $\uparrow$ blood glucose levels.

Biguanides: Biguanides lower blood glucose level by insulin-like effects on the tissues. Mechanism of action is not clear. They are:

- Suppress hepatic gluconeogenesis.
- Inhibit glucose absorption from the intestines.
- Stimulate peripheral uptake of glucose in tissues in the presence of insulin.

Phenformin is not used therapeutically as it causes lactic acidosis. Metformin is safer with lower incidence of lactic acidosis. It does not cause hypoglycemia since it is an euglycemic agent.

- They have insulin-like effects.
- They do not cause hypoglycemia.
- They causes weight reduction - due to anorexia.
- Nausea, diarrhea, metallic taste are transient.
- Preferred in obese diabetics either alone or with sulfonylureas.
- They are contraindicated in renal, hepatic and cardiac diseases.

Adverse effects: Nausea, diarrhea, and metallic taste are self-limiting. Rarely lactic acidosis can occur. Anorexia is advantageous as it helps in reducing body weight. Long-term use may interfere with vitamin B_{12} absorption.

Acarbose

- It is an oligosaccharide that competitively binds to intestinal alpha-glucosidase (the enzyme needed for digestion of carbohydrates) and delays absorption of carbohydrates.
- It should be taken at the beginning of a meal. Flatulence and diarrhea due to the formation of unabsorbed carbohydrates are the principal side effects.

Troglitazone/Pioglitazone/Rosiglitazone

- They increases tissue sensitivity to insulin and potentiates the action of insulin. It thus reduces insulin resistance and hyperglycemia in NIDDM patients.
- In some countries, they are approved for use in cases of insulin-resistance.

Preparations of some oral antidiabetics

Drugs	Doses	Duration of action
Tolbutamide (RASTINON)	500 mg QID	6–8 hr
Chlorpropamide (DIABINESE)	250-500 mg OD	36–45 hr
Glibenclamide (DAONIL EUGLUCON)	5 mg QID	18–24 hr
Metformin (GLYCIPHAGE)	500 mg QID	6–8 hr

Treatment of diabetes mellitus

- The aim of treatment is to keep the blood sugar within normal limits and prevent complications of diabetes. In IDDM, They are treated with insulin alone.
- Mild NIDDM may be controlled by diet, exercise and weight reduction. When not controlled, an oral hypoglycemic should be given.
- Most NIDDM patients may require insulin sometime later in life.

Status of oral antidiabetics

- Uncomplicated NIDDM patients not controlled by diet and exercise are given oral antidiabetic.
- Mild NIDDM patients with recent onset diabetes, age above 40 years at the onset of diabetes, obese with fasting blood sugar < 200 mg/dl are candidates for oral hypoglycemics.
- In such cases sulfonylureas are preferred but, when not adequately controlled, metformin can be added.
- Metformin has the advantages of reducing appetite and being euglycemic. In conditions like stress, surgery or complications of diabetes, insulin should be used.

Therapeutic failure

- If patients are not responding to oral antidiabetics, from the very beginning, it is called **primary failure** and is rare.
- **Secondary failure** of sulfonylureas may result from poor diet control, progression of the disease, or from desensitization of the receptors. In such cases change over to another sulfonylurea or add metformin and if still not controlled, switch over to insulin.
- In some patients, insulin may be supplemented with sulfonylureas as the later increases the tissue sensitivity to insulin.

Insulin is effective in all types of diabetes mellitus. The dose should be adjusted as per the needs of each patient—guided by blood sugar levels.

- Insulin resistance is said to be present when the insulin requirement is increased to > 200 U/day.

It is due to the antibodies to insulin which partly neutralize it.

- This is rare with purified preparations and human insulin. Hence in presence of resistance, change over to highly purified/ human insulin.
- In some patients immunosuppression with corticosteroids like prednisolone may help.

Treatment of diabetic ketoacidosis

- Ketoacidosis may be precipitated by infection, trauma or stress and is more common in IDDM patients.
- Acidosis, dehydration, electrolyte imbalance, impaired consciousness, and hyperventilation are the common features seen.
- Treatment is with regular (plain) insulin by continuous IV infusion (0.1 U/kg/hour).
- After the patient has fully recovered, SC insulin should be administered 30 minutes before stopping the infusion. Fluid and electrolyte replacement are important.

Glucagon: Glucagon is synthesized in the alpha (α) cells of the pancreatic islets of Langerhans; like insulin, the secretion of glucagon is regulated by nutrients—chiefly glucose, paracrine hormones and autonomic nervous system. Fasting stimulates glucagon secretion. It is degraded in the liver, kidney and plasma.

Actions

- Glucagon increases blood glucose level by glycogenolysis and gluconeogenesis in the liver.
- It evokes insulin release.
- It mobilises stored fat and carbohydrates.
- Glucagon increases heart rate and force of contraction. It also relaxes the intestinal smooth muscles.

Uses

1. Severe hypoglycemia – glucagon can be used in the emergency treatment of severe hypoglycemia due to insulin.
2. Diagnostic uses – for diagnosis of IDDM.
3. Radiology of the bowel – as glucagons relaxes intestines.

Corticotropin and The Adrenal Steroids

- Corticotropin (ACTH) stimulates synthesis and release of glucocorticoids (e.g. hydrocortisone) from adrenal cortex (also some androgens).
- Cosyntropin is a synthetic ACTH, which is devoid of allergic manifestation with the retention of biological activity.
- Corticotropin-releasing factor (CRF) from the hypothalamus regulates corticotropin release and is in turn regulated by neural factors and negative feedback effects of plasma glucocorticoids.
- Mineralocorticoid (e.g. aldosterone) release from the adrenal cortex is controlled by the renin-angiotensin system.

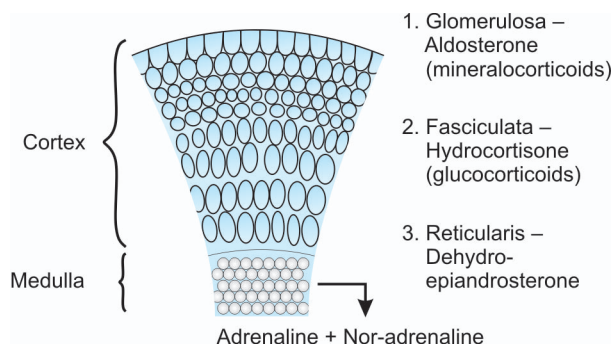


Fig. 8.5.1: Transverse section of adrenal gland

Three important mechanism of regulation of Hypothalamic Pituitary Adrenal axis.

- **Circadian rhythm** : maximum secretion at 3–8 AM, minimum at 6 PM to 12 midnight.
- Negative feedback regulation by steroid.
- Significant rise in the synthesis of steroid due to stress like trauma, pain, surgery, infection, cold, etc.

Corticosteroids

Definition: Corticosteroids are hormones produced in the cortex of the adrenal gland. They are glucocorticoids, mineralocorticoids and a small amount of androgens (Fig. 8.5.1).

- **Adrenal gland** is situated above the kidney. It has two components, one is cortex and other is medulla. The medulla secretes **adrenaline** and **noradrenaline**. The cortex has two zones, the outer zone secretes: **Aldosterone**, while the inner cortical zone secretes: **Androgen** and **Glucocorticoids**.
- Cortisol is the major glucocorticoid while aldosterone is the major mineralocorticoid.

Structure and Synthesis (Fig. 8.5.2)

- The corticosteroids have a cyclopentano-per-hydro-phenanthrene (steroid) ring. They are synthesized in the adrenal cortex from cholesterol under the influence of ACTH.
- Every day about 10-20 mg of hydrocortisone (maximum in the early morning) and 0.125 mg of aldosterone are secreted.
- They are also released in response to stress.

Pharmacological Actions (Fig. 8.5.3)

Glucocorticoid Actions

1. Metabolic effects

On carbohydrates: Decreased uptake and utilization of glucose, and increased gluconeogenesis; this causes a tendency to hyperglycemia.

On proteins: They increased catabolism; reduced anabolism, i.e. they enhance protein breakdown and nitrogen is excreted leading to negative nitrogen balance.

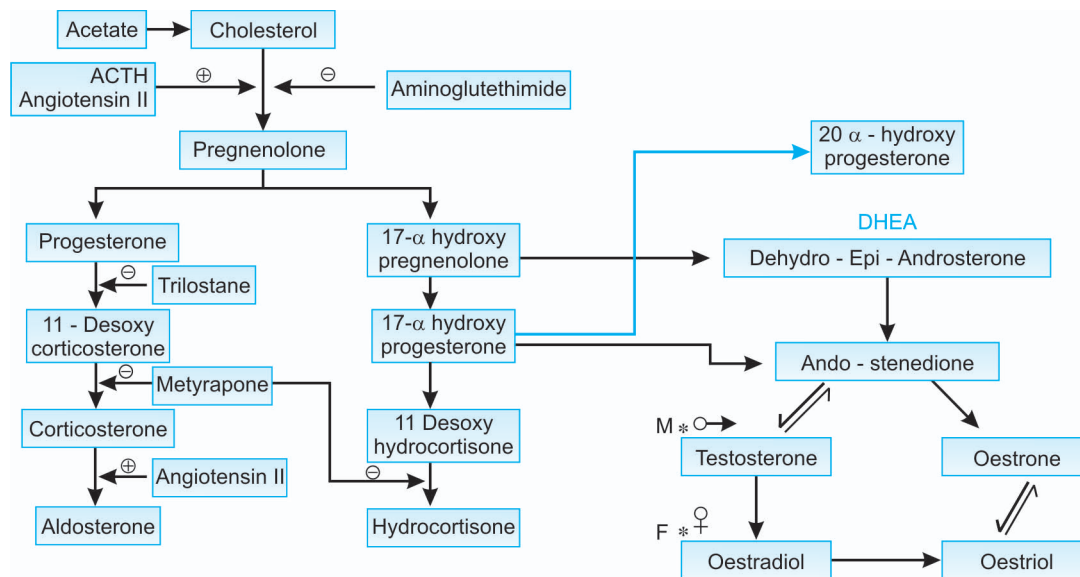


Fig. 8.5.2: Biosynthesis of corticosteroids and adrenal androgen

On fat: They promote lipolysis and redistribution of fat takes place. Fat is mobilized from extremities and deposited over the face, neck and shoulder and excess glucocorticoid activity results in **moon face, fish mouth and buffalo hump** as in Cushing's syndrome.

2. Anti-inflammatory and immunosuppressive effects

Glucocorticoids suppresses the development of inflammatory response to all types of stimuli. They inhibit both early and late manifestations of inflammation.

• On cellular events:

- in areas of acute inflammation: there occurs decreased influx and activity of leukocytes.
- in areas of chronic inflammation: there occurs decreased activity of mononuclear cells, decreased proliferation of blood vessels and less fibrosis.
- in lymphoid areas: decreased clonal expansion of T and B cells and decreased action of cytokine-secreting T cells.

• On inflammatory and immune mediators:

- decreased production and action of cytokines including many interleukins, $\text{TNF}\gamma$, GM-CSF.
- reduced generation of IgG.
- decrease in complement components in the blood.

- In addition glucocorticoids also reduces the synthesis of prostaglandins and leukotrienes by inhibiting phospholipase A_2 .

- Glucocorticoids thus suppress cell-mediated immunity, prevent manifestations of allergy and prevent homograft rejection.
- **Overall effects:** Reduction in chronic inflammation and autoimmune reactions but also decreased healing and diminutions (reduction) in the protective aspects of the inflammatory response.

3. Other actions

Regulatory actions

HPA axis: On hypothalamus and anterior pituitary: a negative feedback action resulting in reduced release of endogenous glucocorticoids.

CNS: They are required for normal functioning of the central nervous system. Deficiency results in apathy and depression while large doses result in restlessness, anxiety and sometimes psychosis.

CVS: On vascular events: reduced vasodilatation; decreased fluid exudation. Glucocorticoids reduce capillary permeability, maintain the tone of arterioles and have a positive inotropic effect. Prolonged use can cause hypertension.

Skeletal muscles: They are essential for normal muscular activity. Deficiency leads to fatigue and weakness.

GIT: Glucocorticoids enhance the secretion of gastric acid and pepsin in the stomach.

Growth: With chronic use may have potential for growth retardation in children.

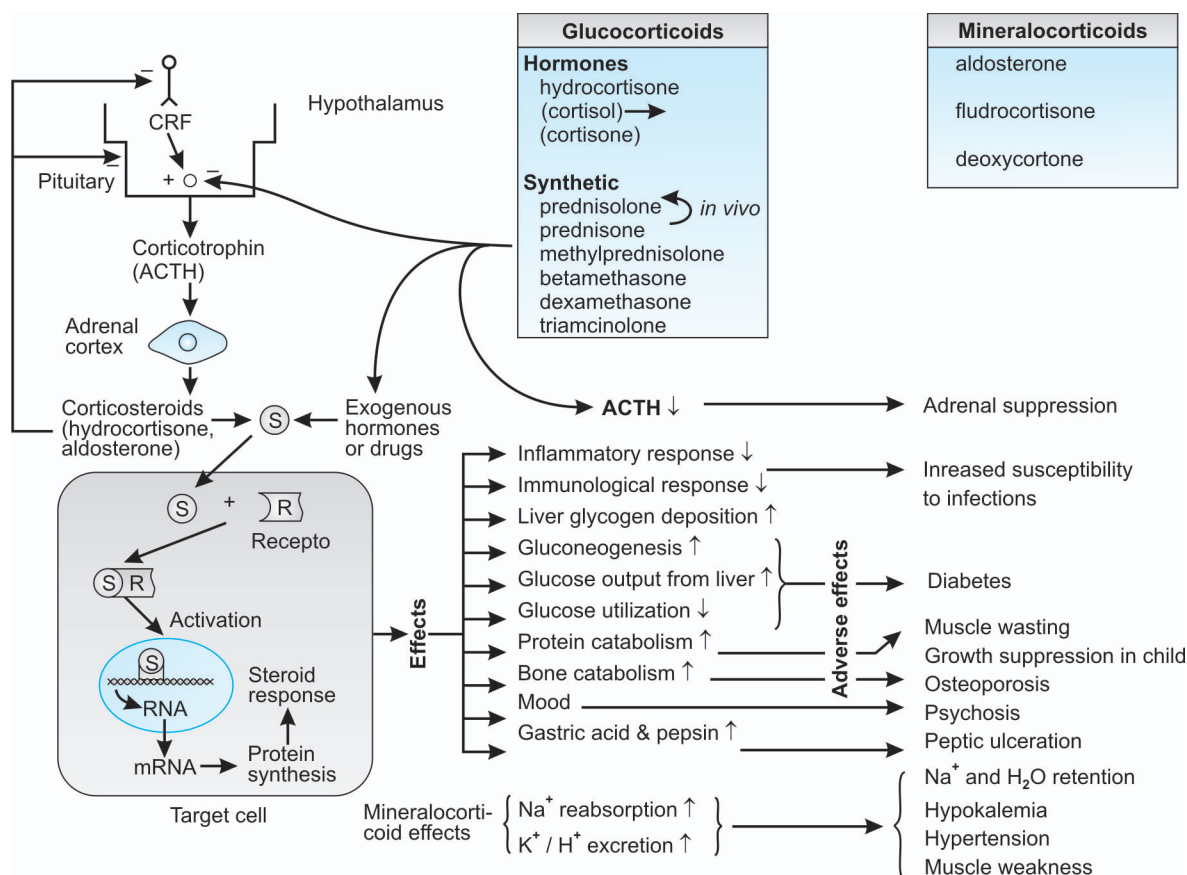


Fig. 8.5.3: Mechanism of action and actions of glucocorticoid and mineralocorticoids

Calcium metabolism: Glucocorticoids *inhibit absorption and enhance the renal excretion of calcium*, they antagonize the effect of vitamin D on calcium absorption. Bone resorption takes place (negative calcium balance)

Formed elements of blood: Glucocorticoids have a lymphocytic effects which is very prominent in lymphomas. They also increase the number of platelets and RBCs.

They are essential for maintaining normal GFR.

Glucocorticoids (drugs) for the therapeutic indications:

Hydrocortisone, prednisolone and dexamethasone.

Mineralocorticoid action: Glucocorticoids have a weak mineralocorticoid action – *cause some salt and water retention and potassium excretion*. **Some synthetic glucocorticoids are devoid of this activity.**

Mechanism of action of the glucocorticoids: Glucocorticoids interact with specific intracellular receptors in the

cytoplasm; resulting with DNA to modify gene transcription-inducing synthesis of some proteins and inhibiting synthesis of others (Fig. 8.5.3).

- For metabolic actions, most mediator proteins are enzymes, e.g. cAMP-dependent kinase, but not all actions on genes are known.
- For anti-inflammatory and immunosuppressive actions, some actions at the level of the genes are known :
 - inhibition of transcription of the genes for COX-2, cytokines (e.g. the interleukins) cell Ultimately ↓ in ELAM-, ICAM-1 in endothelial cell
 - blockade of vitamin D₃-mediated induction of the osteocalcin gene in osteoblasts and modification of transcription of the collagenase genes and stromolysin genes.
 - Increased synthesis of lipocortin 1, in macrophages, endothelium and fibroblasts which is important in negative feedback on hypothalamus and anterior pituitary and may have anti-inflammatory actions.
 - Inhibit IgE mediated histamin and LT-C4 release from basophils.

Pharmacokinetics and unwanted actions of the glucocorticoids:

- Most glucocorticoids are well-absorbed orally. Administration: **oral, topical and parenteral**; 90% bound to plasma protein. The drugs are bound to *corticosteroid-binding globulin* (transcortin) in the blood and enter into cells by diffusion.
- Hydrocortisone undergoes high first pass metabolism by microsomal enzymes in the liver and are excreted by kidneys.
- The $t_{1/2}$ varies with each agent and are short, intermediate and long-acting. On an average half-lives is about 1.5 hours.
- Unwanted effects are seen mainly with prolonged systemic use as anti-inflammatory or immunosuppressive agents (in which all the metabolic actions are unwanted), but no adverse effect usually with replacement therapy.

Preparations (Table 8.5.1 and 8.5.2)

Several glucocorticoid preparations are available for topical use as creams, ointments, nasal and eye drops. Some

of them also contain antibiotics. Other important preparations are:

- **Short acting ($t_{1/2}$: 8–12 hours):** Cortisone, Corticosterone, Fludrocortisone, etc.
- **Intermediate acting ($t_{1/2}$: 12–36 hours):** Prednisone, Prednisolone, Methyl prednisolone, etc.
- **Long acting ($t_{1/2}$: 36–72 hours):** Betamethasone, Dexamethasone.

Table 8.5.2: Some topical glucocorticoid preparations

Hydrocortisone (LYCORTIN Oint)	1%
Triamcinolone (LEDERCORT ACETONIDE Oint)	0.1%
Dexamethasone (DECADRON Cream)	0.1%
Flucinolone acetamide (FLUCORT Oint)	0.025%
Betamethasone (BETNOVATE Oint, Cream)	0.025%
Beclomethasone dipropionate (BECLATE Cream)	0.025%
Clobetasol propionate	0.05%

Table 8.5.1: Preparations and dose of some commonly used glucocorticoids

Glucocorticoid	Trade name	Dosage form	Daily dose
Hydrocortisone hemisuccinate	Efcortin	10 mg tablet 50 mg/ml inj IM, IV	30-100 mg
Prednisolone	Wysolone	5, 10 mg tab 20 mg/ml inj IM	5-60 mg
Methyl-prednisolone acetate	Solumedrol	4 mg tab 20 mg/ml inj	4-32 mg
Triamcinolone	Kenacort	4 mg tab 10 mg/ml inj 5-40 mg inj IM/IA	4-20 mg
Betamethasone	Betnesol (4 mg/ml/inj) →	0.5 mg tab 4-20 mg IM/IV	0.5-5 mg oral
Dexamethasone	Dexona (4 mg/ml/inj) →	0.5 mg tab 4-20 mg IV/IM	0.5-5 mg oral
Fludrocortisone	Floricort	100 mcg tab	50-200 mg/day
Desoxycorticosterone acetate (DOLA)	Docabolin	10 mg/ml inj	2-5 ml sublingual 10-20 mg in once/week

IM = intramuscular; IV = intravenous; IA = intra-articular

- Prednisolone has potent glucocorticoid activity with mild mineralocorticoid activity. It is the most commonly used preparation.
- Prednisone is a prodrug converted to prednisolone in the liver.
- Hydrocortisone, the chief natural glucocorticoid is generally used orally and parenterally; but in the management of emergencies, it is used intravenously.
- Methyl-prednisolone is similar to prednisolone and is used as retention enema and for high dose pulse therapy.
- Triamcinolone, dexamethasone, betamethasone have no mineralocorticoid activity and have selective, potent glucocorticoid effects.

Some of the inhalational steroids are enlisted in Table 8.5.3.

Table 8.5.3: Inhalation steroids

Beclomethasone (BECLATE INHALER)	50 mcg, 100 mcg 200 mcg/metered dose
Budesonide (BUDECORT)	200 mcg/metered dose
Fluticasone (FLOHALE)	25, 50, 150 mcg/ metered dose

Therapeutic Uses

Replacement therapy (endocrinal conditions):

- **Acute adrenal insufficiency (Addisonian crisis):** It is an emergency condition. It may result from fulminating infection, trauma, hemorrhage or sudden withdrawal of steroids. Clinical features are fever, myalgia, arthralgia, dehydration and hypotension. Management includes: Intravenous hydrocortisone hemisuccinate 100 mg bolus followed by infusion is given immediately. Once the patient recovers, switch over to oral preparations. **Correction of fluid and electrolyte balance are important.**
- **Chronic adrenal insufficiency (Addison's disease):** It is due to destructive lesions of adrenal gland that may be resulted due to surgery, TB, AIDS, autoimmune diseases, etc. Oral hydrocortisone 20-40 mg daily is given. Some patients may need additional fludrocortisone (a mineralocorticoid)
- **Congenital adrenal hyperplasia:** It is due to deficiency of enzyme 21 hydroxylase which is required for steroid synthesis.

Glucocorticoids have been used in a variety of **non-endocrinal conditions** where they are of palliative value, but may even be life saving.

These are:

1. **Rheumatoid arthritis:** In progressive disease steroids are given with NSAIDs.
2. **Bronchial asthma**
 - Acute exacerbations: a short course of prednisolone (40 mg in divided doses for 5 days)
 - Status asthmaticus: intravenous hydrocortisone hemisuccinate.
 - Chronic asthma: steroids are used as supplement to bronchodilators. Inhalational steroids are used.
3. **Osteoarthritis:** Steroids given as intra-articular injections.
4. **Rheumatic carditis:** Severely ill-patients with fever and not responding adequately to NSAIDs require glucocorticoids.
5. **Acute gout:** prednisolone is used as an adjuvant with NSAIDs
6. **Allergic diseases:** Like angioneurotic edema, hay fever, serum sickness, contact dermatitis, urticaria, drug reactions and anaphylaxis: steroids are indicated. Steroids are slow acting and in less severe cases, antihistaminics should be preferred.
7. **Skin diseases:** Atopic dermatitis, seborrhic dermatitis, inflammatory dermatoses and other local skin conditions are treated with topical steroids. Systemic steroids are life saving in pemphigus.
8. **Collagen diseases:** Like polyarthritis nodosa, lupus erythematosus, polymyositis, Wegener's granulomatosis and other rheumatoid disorders.
9. **Eye diseases:** Allergic conjunctivitis, uveitis, optic neuritis and other inflammatory conditions are treated with steroids. *In ocular infections, steroids are contraindicated.*
10. **Renal diseases:** Like nephrotic syndrome are treated with steroids.
11. **Gastrointestinal diseases:** Mild inflammatory bowel diseases like ulcerative colitis are treated with steroid enema while severe cases need oral prednisolone.
12. **Liver diseases:** Steroids are useful in conditions like chronic active hepatitis and alcoholic hepatitis.
13. **Hematological disorders:** Like purpura and hemolytic anemia having immunological etiology respond to steroids.
14. **Cerebral edema:** Large doses of dexamethasone is given.
15. **Malignancies:** Steroids are used in treatment of acute lymphocytic leukemia, lymphomas and breast cancer, etc.
 - In neoplastic disease
 - in combination with cytotoxic drugs in treatment of specific malignancies (e.g. Hodgkin's disease, acute lymphocytic leukemia)

- to reduce cerebral edema in patients with metastatic or primary brain tumors (dexamethasone is the drug used)
- as a component of anti-emetic treatment in conjunction with chemotherapy.

16. Lung diseases: Apart from **bronchial asthma**, steroids are used in other diseases like aspirational pneumonia and presentation of infant *acute respiratory distress syndrome*. [ARDS]

17. Organ transplantation: For prevention and treatment of graft rejection.

Adverse effects of glucocorticoids: Advers effects of glucocorticoids are depends on dose, duration of therapy and the relative potency of additional mineralocorticoid effects. Whenever possible, they should be used topically to avoid systemic effects. Single doses are harmless while short courses are well-tolerated. Prolonged use is associated with toxicity. Adverse effects include:

1. **HPA axis suppression:** Depends on the dose, duration and time of administration. After prolonged steroid therapy, adrenal cortex gradually atrophies due to feedback inhibition. If steroid administration is suddenly stopped, acute adrenal insufficiency results.
2. **Cushing's syndrome** with characteristic appearance of moon face, buffalo hump, central obesity, muscle wasting, thinning of the limbs and skin, easy bruising, purple striae and acne (Fig. 8.5.4).

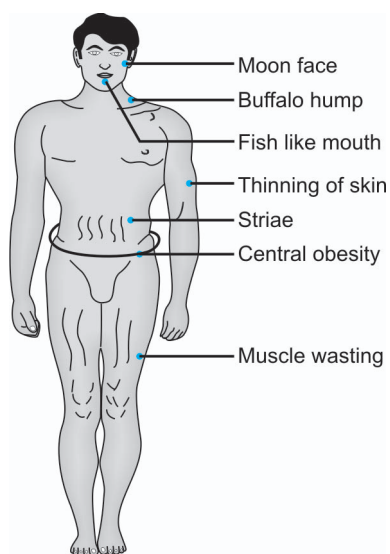


Fig. 8.5.4: Cushing syndrome

3. **Hyperglycemia** and sometimes diabetes mellitus may be precipitated.
4. **Susceptibility to infection** is increased.
5. **Osteoporosis** more common in the elderly.
6. **Avascular necrosis** of the bone due to restriction of blood flow through bone capillaries may cause pain and restriction of movement.
7. **Peptic ulceration** may sometimes occur on prolonged therapy especially when other ulcerogenic drugs are (e.g. NSAIDs) used concurrently.
8. **Mental disturbances** like euphoria, psychosis or depression can occur.
9. **Cataract** and glaucoma may follow long-term use of glucocorticoids even as eye drops.
10. **Delayed wound healing:** Steroids may delay wound healing.
11. **Other effects** include raised intracranial pressure, convulsions, hypercoagulability of the blood and menstrual disorders.
12. **Mineralocorticoid effects** including salt and water retention, edema, hypokalemia and hypertension are rare with selective glucocorticoids.

Contraindication to glucocorticoid therapy

Steroids should be used with caution in:

- | | |
|----------------------|-------------------|
| 1. Peptic ulcer | 6. Psychoses |
| 2. Hypertension | 7. Epilepsy |
| 3. Infections | 8. CCF |
| 4. Diabetes mellitus | 9. Glaucoma |
| 5. Osteoporosis | 10. Renal failure |

Principles to guide steroid therapy:

- A single dose (even the larger one) is actually harmless.
- Appropriate dose of steroid is determined by trial and error basis.
- In the absence of any specific contraindication, a few days of therapy is usually harmless.
- Except in adrenal insufficiency, where steroid replacing the deficit, usually it play a palliative role.
- The risk of adrenocortical suppression is greater with the dose exceeding physiological amount. The risk is less if it will be administered with biological clock, i.e. if given in the morning, and even less if alternate morning therapy is used.
- Dose must need to be increased in the patients who are on steroids, and faces any trauma, stress, surgery, etc.
- There may be risk of life threatening adrenal insufficiency if steroid therapy is suddenly stopped after a

prolonged period. It should be stopped in tapering fashion. Short courses up to 40 mg/day for a week may be stopped suddenly.

- Do not start steroid if there is infection except certain specific situations, where it can be started under coverage of specific antimicrobial agents. If patient is already on steroid therapy, do not stop it, rather increase the dose along with addition of specific and effective antimicrobial agent with it.
- Supplement steroidal therapy with calcium, vitamin D and bisphosphonates to reduce the risk of osteoporosis.
- Patient must be informed regarding:
 - Problems of abrupt withdrawal
 - Reporting of puffiness, weight gain, edema, muscle weakness, black tarry stool, fever, throat infection, etc.

MINERALOCORTICOIDS

- The most important natural mineralocorticoid is aldosterone synthesized in zona glomerulosa of the adrenal cortex. Small amounts of desoxycorticosterone is also released.

- Actions: Mineralocorticoids promote sodium and water retention by distal renal tubules with loss of potassium.

Adverse effects: Include weight gain, edema, hypertension and hypokalemia.

Fludrocortisone: is given orally to produce a mineralocorticoid effect. This agent:

- Increase Na^+ reabsorption in distal tubules and increases K^+ and H^+ efflux into the tubules.
- It acts, like most steroids, on intracellular receptors that modulate DNA transcription causing synthesis of protein mediators.
- It is used with a glucocorticoid in replacement therapy.

Inhibitors of Adrenal Steroids Synthesis

Metyrapone, trilostane, aminoglutethimide, ketoconazole, mifepristone, and mitotane.

- These drugs inhibit the synthesis of adrenal steroids by inhibiting certain enzymes involved in steroid synthesis.
- They are used in Cushing's syndrome and some prostatic and breast cancers.

6

PHYSIOLOGICAL CONSIDERATION: Hormonal control of the female reproductive system.

- At puberty, the menstrual cycle starts with menstruation which stretches over 30-40 years characterized by regular episodes of uterine bleeding.
- The hypothalamus releases the GnRH in pulses.
- Hypothalamic GnRH acts on the anterior pituitary to release the gonadotrophins, FSH and LH, which act on the ovary.
- The gonadotrophins stimulate follicle development. FSH is the main hormone stimulating estrogen release.
- Just before the midcycle, the estrogen secretion reaches a peak, stimulating a brief surge in FSH and **LH** levels which results in **ovulation** by around the 14th day of the cycle.
- LH is the main hormone controlling subsequent progesterone secretion from the corpus luteum.
- Estrogen controls the proliferative phase of the endometrium and has negative feedback effects on the

anterior pituitary. Progesterone controls the later secretory phase and has negative feedback effects on both hypothalamus and anterior pituitary.

- If fertilization occurs the fertilized ovum is implanted, the corpus luteum continues to secrete progesterone during the pregnancy.
- If fertilization does not occur; progesterone secretion stops and again menstruation starts.

ESTROGENS: The estrogens are produced by the ovaries, placenta and in small amounts by the adrenals and testes (Table 8.6.1 and Fig. 8.6.1).

- **Natural estrogens:**

<i>Potency</i>	Estradiol,	Estriol,	Estrone
	100	: 10	: 1

- **Steroidal estrogens:** Ethinyl estradiol, Tibolone, and Mestranol.
- **Nonsteroidal:** Diethyl stilbestrol, Dienestrol and Hexestrol.

Table 8.6.1: Secretion and synthesis of estrogen

Synthesis of estrogen	Secretion
Acetate	Hypothalamus
↓	↓
Cholesterol	Periodic release of GnRH
↓	↓ anterior pituitary
Pregnenolone	FSH and LH
↓	↓
DHEA (dehydroepiandrosterone)	Growth and maturation of Graffian follicle in ovaries
↓	↓
Androstenedione	Secretion of estrogen and progesterin by ovaries
↓	
Testosterone → Estradiol → Estrone	
↓	
Estril	

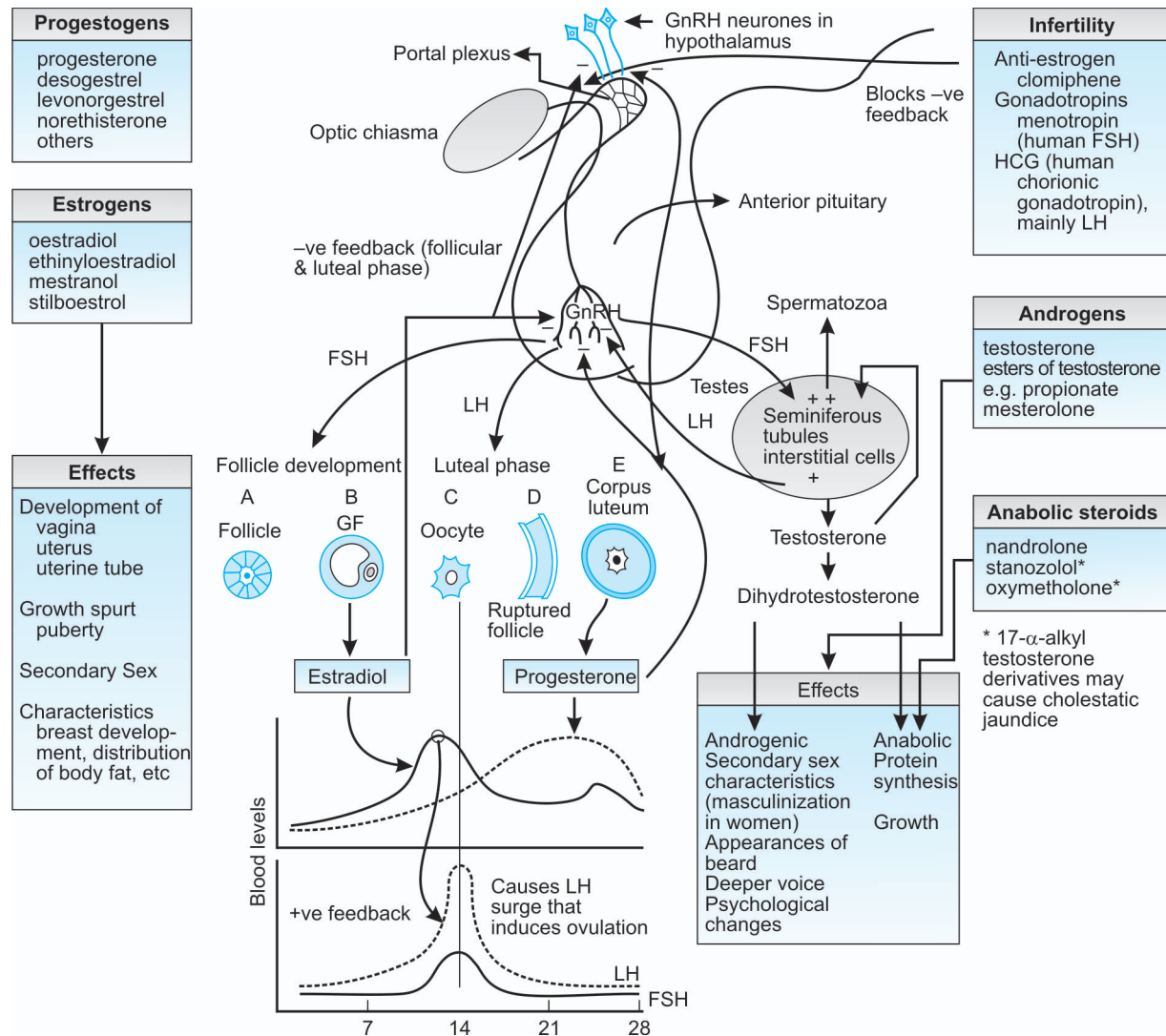


Fig. 8.6.1: Secretion and action of estrogen and progestin

Actions of Estrogens (Fig. 8.6.1)

- Growth:** for normal maturation of the female reproductive tract, endometrium and activity of mammary glands.
- Development of secondary sexual characters in the female.
- It prepare the endometrium for progesterone action (estrogen priming).
- It prepare uterus for sperms transport.
- It regulate secretion of Gonadotropins.
- Estrogens inhibit the resorption of bone and maintain the bone mass. They promote the fusion of epiphyses. It induces mild anabolism.

- Estrogens are important for the maintenance of normal structure of the skin and blood vessels in women.
- Estrogens decrease plasma LDL cholesterol and raise HDL cholesterol and triglycerides.
- Estrogens enhance the coagulability of the blood and increases vascular permeability and tissue edema.

Pharmacokinetics

- Natural estrogens are metabolized rapidly in the gut therefore not effective orally; All estrogens get absorbed through the skin and mucous membrane. Synthetic estrogens are orally effective and are long-acting.
- They are largely bound to plasma proteins.
- They have a short $t_{1/2}$.

Preparation: Estrogens are available for oral and parenteral use. A transdermal patch for cyclic estrogen therapy is also available.

Therapeutic Uses

1. Hormone replacement therapy (HRT) in Postmenopausal syndrome:

Hormone replacement may be beneficial in:

- Prevention of bone loss.
- Prevention of vasomotor symptoms like: hot flush, sweating, paresthesia and chill sensation.
- Protection against cardiovascular complication.
- Prevention against urinogenital atrophy and changes.
- Delaying onset of alzheimer's disease.
- Decreases postmenopausal sleep disturbances
- Improvement in feeling of well-being.

2. Replacement therapy in primary hypogonadism: Estrogen started at 11-13 years of age stimulates the development of secondary sexual characters and menstruation in females.

3. Senile vaginitis is common in elderly women due to estrogen withdrawal from ovary.

4. Osteoporosis: Specially in postmenopausal osteoporosis, it is a drug of choice.

5. As oral contraceptives: Various preparations are available.

6. Dysmenorrhea: Estrogens combined with progestins, suppress ovulation and such anovulatory cycles are painless.

7. Dysfunctional uterine bleeding (DUB): Estrogens are used as an adjuvant to progesterone.

8. In treatment of carcinoma prostate.

Adverse effects:

- Nausea, migraine headaches, hyper-pigmentation, hypertension, breast tenderness and cholestasis may be seen.
- In men gynecomastia and feminization may occur.
- On long-term estrogen therapy, increased incidences of endometrial and breast cancers are reported
- **Teratogenic:** When given to a pregnant lady estrogens may cause:
 1. *In male child:* genital abnormalities
 2. *In female child:* increased risk of cervical and vaginal cancers

Contraindications: Estrogen dependent tumors, liver disease, thromboembolic disorders, etc. are the important contraindications of estrogens.

ANTIESTROGENS

Clomiphene citrate and cyclofenile

- It binds to the estrogen receptors and acts as a competitive inhibitor of endogenous estrogens.

- Clomiphene induces gonadotropin secretion and thereby induces ovulation by blocking the negative feedback of endogenous estrogens on the hypothalamo-pituitary axis.

Side effects: It includes ovarian hyper-stimulation resulting in multiple pregnancy, ovarian cysts, hot flushes, headache and skin rashes.

Therapeutic Indications

1. Infertility in females: Clomiphene citrate is used in infertility due to ovarian disorders.

2. In vitro fertilization: Clomiphene induced ovulation is also useful in *in vitro* fertilization.

3. In the treatment of oligozoospermia in male.

Tamoxifen

- It binds to the estrogen receptors and competitively block the binding of estrogens to its receptor. It is also a partial agonist at certain tissues. Side effects include hot flushes, nausea, vomiting, vaginal bleeding and skin rashes.
- **Doloxifene and Raloxifene are under clinical trial.**

Therapeutic Uses

1. Breast cancer: Palliation of advanced breast cancer in postmenopausal women with estrogen receptor-positive tumors

2. In the treatment of male infertility.

PROGESTINS

- Progesterone is the natural progestin.
- It is a 19-Nor testosterone derivatives.
- It is synthesized in the corpus luteum of ovary in second half of menstrual cycle, in placenta, in testis and in the adrenals where, it acts as a precursor of various steroid hormones.

Classification:

Natural: Progesterone

Synthetic: Medroxyprogesterone acetate, Hydroxyprogesterone coproate, Megestrol (Newer: Nomegestrol), Allylestrenol, Norethisterone acetate, Lynestrenol, Ethynodiol diacetate, Norgestrel, Norgestimate and Desogestrel (newer agents).

Mechanism of action: It is just like other steroidal hormone but with stimulation of progestin receptors.

Actions (See Fig. 8.6.1)

Maintenance of Pregnancy by:

- **Decreasing uterine motility.**
- **By reducing immunological rejection of fetus.**

Uterus: In the endometrium, there occurs changes like increased tortuosity of the glands, hyperemia and increased secretions. Progesterone is very important for the maintenance of pregnancy (Progestin=favors pregnancy).

Cervix: The watery cervical secretion is changed to a **viscid scanty secretion** by progesterone.

Vagina: Vaginal epithelium changes and leukocyte infiltration are seen in pregnancy.

Mammary gland: Along with estrogen, progesterone is responsible for the development, i.e. proliferation of the acini in the breast and prepares the gland for lactation.

Body temperature: There is mid cycle increase in the basal body temperature by 1 degree centigrade during luteal phase at ovulation is due to progesterone.

CNS: Sedative effect

Respiration: Stimulatory effect of respiration.

Metabolism: Decreases HDL level (dangerous)

Pituitary gland: Weak inhibitory effect on gonadotropin secretion.

Adverse effects

- Headache, breast engorgement, rise in body temperature, edema, acne and mood swings may be important adverse effects.
- It also shows teratogenic effect.

Therapeutic Indications (Table 8.6.2)

- As oral Contraceptive
- **In Hormone replacement therapy (HRT):** Progestins are combined with estrogens in HRT of postmenopausal women given cyclically.
- **In menstrual disorder like:** Premenstrual tension (PMT), dysfunctional uterine bleeding (DUB), and amenorrhea.
- **Ovarian suppression:** Progestins are used to suppress ovulation in dysmenorrhea.
- **Threatened or habitual abortion:** Efficacy in such patients is not proved.
- **Endometriosis**
- **Endometrial carcinoma:** Progestins are used as a palliative measure in cases with metastasis.
- **For suppression of postpartum lactation.**
- **For treating hypoventilation in obese patient and for Postponement of menstruation.**

Table 8.6.2: Therapeutic uses of estrogens and progestins

Estrogens	Progestins
1. HRT: – Primary hypogonadism – Postmenopausal syndrome	1. HRT
2. Contraceptive	2. Contraception
3. Senile Vaginitis	3. Dysmenorrhea
4. Osteoporosis	4. DUB
5. Carcinoma prostate	5. Endometriosis
6. DUB	6. Premenstrual tension
7. Dysmenorrhea	7. Endometrial cancer

Benefits of combined pills

- Effective and convenient method of contraception.
- Reduced risk of ovarian and endometrial cancers.
- Reduced incidence of pelvic inflammatory disease and ectopic pregnancy.
- **Menstrual benefits**—less menstrual blood loss, less iron-deficiency; less premenstrual tension and dysmenorrhea.

Contraindications to combined pill

- Thromboembolic and cerebrovascular disease
- Breast cancers
- Liver disease
- Oral contraceptives should be used with caution in *hypertension, diabetes, convulsive disorders, edema and CCF*.

ANTIPROGESTINS

Mifepristone

- 19 Nor-steroid with potent competitive anti-progestational and anti-glucocorticoidal activity
- When given in early pregnancy - abortion occurs.

Mechanism of action

- Mifepristone blocks the progesterone receptors in the uterus which causes decidual breakdown; blastocyst gets detached, *HCG and progesterone secretions fall*.
- This in turn increases prostaglandin levels and stimulate uterine contractions. It also softens the cervix and facilitates expulsion of the blastocyst.
- If given during the follicular phase; it prevents the midcycle surge of gonadotropins and delays ovulation.
- Mifepristone also binds to glucocorticoid receptors.

Therapeutic Indication

- **Termination of pregnancy:** Pregnancy up to 2 months can be terminated with a single oral dose: 600 mg of mifepristone followed 48 hours later by a prostaglandin to increase uterine contractions and facilitate expulsion of the blastocyst.
- **Adverse effects** include heavy bleeding, nausea and abdominal pain.
- **Postcoital contraceptive:** Mifepristone prevents implantation when given within 72 hours after coitus.
- **Induction of labor**
- **Cushing syndrome.**

HORMONAL CONTRACEPTIVES (Table 8.6.3)

- Oral contraceptives are the agents used orally to prevent conception.
- When properly used, they are the most effective spacing method of contraception.
- An ideal contraceptive must have reversibility, acceptability, simplicity, efficacy, less toxicity and low cost.
- Hormonal contraceptives have greatly contributed to the control of the population throughout the world.

Oral pills	Depot preparations
1. Combined pills	1. Injectables
2. Mini pills	2. Subcutaneous implants
3. Postcoital pills	

Combined pills (classical or balanced): They contain low doses of an estrogen and a progestin. They are highly efficacious (success rate 98%).

- The combined pill contains an estrogen and a progestogen. It is taken for 21 consecutive days out of 28. Ethinylloestradiol or mestranol (in the dose of 30-50 mcg) is the estrogens used, while 0.5 to 2.5 mg of levonorgestrel or norgestrel, or desogestrel or lynestrenal is used. This is monophasic regimen.
- **Mode of action:** The estrogen inhibits FSH release and therefore also inhibits follicle development; the progestogen inhibits LH release and therefore ovulation; and makes cervical mucus inhospitable for sperm; together they render the endometrium unsuitable for implantation.
- **Drawbacks:** Weight gain, nausea, mood changes and skin pigmentation can occur.
- **Serious unwanted effects** are rare. A small proportion of women develop reversible hypertension; there is evidence for an increased risk of breast cancer; there is a small increased risk of thromboembolism with third-generation pills.
- There are several beneficial effects, not least the avoidance of unwanted pregnancy which itself carries a insignificant risk.
- If a woman misses a pill, she should take 2 pills on the next day and continue the course.
- If more than 2 pills are missed, then that course should be withdrawn, should follow an alternate method of contraception for that particular cycle and restart the course on the 5th day of the next menstrual cycle.
- If the woman has conceived, the pregnancy should be terminated as these hormones are teratogenic.

Oral contraceptives are also available as biphasic or triphasic preparations. This reduces the amount of hormones needed and more closely mimics menstrual cycles.

Table 8.6.3: Oral contraceptive preparations

Regimen	Estrogen	Progestin	
Monophasic	Ethinyl estradiol 50 (mcg) Ethinyl estradiol 30 (mcg)	Norgestrel 0.5 mg Levonorgestrel 0.15 mg	OVRAL-G OVRAL-L
Biphasic	Ethinyl estradiol 35 (mcg)	Norethindrone: 0.5 mg (10 days) 1 mg (11 days)	
Triphasic	6 days Ethinyl estradiol 30 (mcg) next 5 days Ethinyl estradiol 40 (mcg) next 5 days Ethinyl estradiol 30 (mcg)	Levonorgestrel 50 (mcg) Levonorgestrel 75 (mcg) Levonorgestrel 125 (mcg)	TRIQUILAR
Mini-pill	Nil	Norgestrel 75 (mcg)	OVRETTE
Postcoital pill	Diethyl stilbestrol or Levonorgestrel (0.25 mg - 0.7 mg/day for 5 days) or Combined pill (2 stat and 2 after 12 hours)	—	—

Mini-pill

The progestogen-only pills: The progestogen-only pill is taken continuously. It differs from the combined pill in that the contraceptive effect is less reliable and is mainly due to the alteration of cervical mucus. Irregular bleeding is likely to occur. It does not interfere with lactation.

Postcoital pill or emergency pills

- High dose of an estrogen, diethylstilbestrol or ethyl estradiol, was used twice a day for 5 days earlier.
- The combination is now preferred due to lower doses and lesser side effects.
- The pill should be started within 72 hours of coitus and has an efficacy of 90-98%. It is advocated as an emergency method in situations following rape or contraceptive failure.
- If ineffective, termination of pregnancy is planned, since because there is risk of vaginal carcinoma in female offspring.

Injectable/Depot preparations are given as:

- **Long acting progestin alone:**
 - (DMPA) Depot medroxy-progesterone acetate 150 mg, intramuscularly at 3-6 months interval or
 - (NEE) Norethisterone enanthate 200 mg intramuscularly at 2 month intervals.
- **Long acting progestin + long acting estrogen:** intramuscularly once a month
- **Implants:** They are implanted under the skin.
 - Norplant capsules implanted subcutaneously in the forearm or upper arm work for 5 years.

Disadvantages: I. Amenorrhea is frequent
II. Permanent sterility may occur.

Mechanism of Action of Oral Contraceptives

- The (OCs) oral contraceptives blocks the release of gonadotropins from the pituitary and thereby **inhibits ovulation**.
- Thickening of cervical mucus secretions.
- Made endometrium hyperproliferative and hypersecretory, which is not suitable for **nidation**.
- Increases uterine contraction (**disfavor fertilization**).
- **Causes dislodgement** of implanted blastocyst.

Adverse effects

- Nausea, vomiting, headache, breast tenderness,
- Spotting and amenorrhea and irregular menstrual cycles may be commonly seen.
- Weight gain, acne, mood swings and hirsutism may occur.
- More severe side effects include: cardiovascular effects (in women > 35 years) there is an increased risk of MI and venous thromboembolism.
- Increased incidence of cervical, breast and other cancers.
- Incidence of cholestatic jaundice and gallstones may be higher.

Nonsteroidal estrogen antagonist

Centchroman (SAHELI): A chroman derivative is a non-steroidal oral contraceptive developed by **CDRI**, Lucknow, India.

- It has antiestrogenic as antiprogesterogenic activity and may act by preventing implantation.
- Onset of action is quick (< 60 minutes) and duration of action is 7 days.
- Dosage (SAHELI, CENTRON) 30 mg twice a week for 3 months followed by once a week till contraception is desired (The tablet should be continued without withdrawing during menstruation).

Centchroman has the following advantages:

1. Success rate claimed to be 97-99%
2. It is devoid of the side effects of hormonal contraceptives
3. Long $t_{1/2}$ allows once a week administration
4. No teratogenicity, carcinogenicity or mutagenicity reported till now.
5. It is well tolerated.

Adverse effects

- **Centchroman** may cause prolongation of menstrual cycles in 10% of women.
- It may cause ovarian enlargement and should be avoided in polycystic ovaries.
- It should also be avoided in renal and hepatic dysfunction, tuberculosis and in lactating mothers.

Androgens and Anabolic Steroids

- Endocrine secretions from the hypothalamus, pituitary and gonads control the male reproductive system.
- Testes are endocrine gland : **Berthold 1849**
- **Testosterone** is the most important natural androgen.
- **Androgens** are produced primarily in the testis and small amounts in the adrenal cortex.

Classification of Androgen

• Natural androgen

Testosterone $\xrightarrow{\quad\quad\quad}$ Dihydrotestosterone
 $\quad\quad\quad 5\alpha\text{-reductase (more active)}$

- Metabolite of testosterone $\xrightarrow{\quad\quad\quad}$ Androsterone
- **Weak androgen:** Dihydroepiandrosterone and androstenedione
- **Synthetic androgens:** Methyl-testosterone, fluoxymesterone, testosterone undecanoate and mesterolone.
- In the adult male, 3-12 mg of **testosterone** is produced daily. Its secretion is regulated by gonadotropins and GnRH.
- Plasma level of testosterone in male = 1 mcg/dl and in female = 50 ng/dl.
- In the females, small amounts of androgens are produced in the ovary and adrenal cortex.

Regulation of Secretion: GnRH from the hypothalamus acts on the anterior pituitary to release both FSH, which stimulates gametogenesis, and LH (also called interstitial cell-stimulating hormone) which stimulates androgen secretion.

Inhibin: It is a non-steroidal (protein) substance produced by testes, inhibit gonadotropin release (specially FSH).

Physiological actions

- In the male, testosterone is essential for the development of secondary sexual characters and sex organs like : *genitalia growth, pubic hair, skin thickening, sebaceous gland proliferation, heavy voice, development of male behavior and phenotype.*
- It is necessary for development of **testes**; normal spermatogenesis and is important for maintaining sexual function in men.
- **Skeletal muscles/Skeleton:** Testosterone promotes bone growth, epiphyseal fusion, enhances the muscle building, salt and water retention, protein synthesis and positive nitrogen balance. It has anabolic actions.
- It is responsible for euphoria, wellbeing and also increases erythropoiesis

Mechanism of action: Its action are through cytoplasmic receptor mediated. It is similar to other steroids. Androgens bind to androgen receptors on the target cells, the complex moves to the nucleus where it stimulates DNA for transcription and the m RNA moves out and ultimately $\uparrow$ translation (protein synthesis) in ribosomes.

Uses

- **Testicular failure:** Testosterone is used in **Androgen replacement therapy** in primary and secondary testicular failure.
- In the treatment of Hypopituitarism.
- In angioneuratic edema
- **Other uses:** Androgens may be used in senile osteoporosis and **carcinoma of the breast** in premenopausal women and in the treatment of Menstrual syndrome.

Adverse effects

- Virilization (masculinization) and acne in females.
- Hepatotoxicity (cholistatic jaundice).
- Increased libido and precocious puberty can occur in young boys.
- With large doses, salt and water retention, suppression of spermatogenesis (Oligozoospermia) resulting in infertility in males.

- Feminizing effects like gynecomastia in men can occur as some androgens are converted to estrogens.

Note: Androgen is contraindicated in patients of carcinoma prostate

ANABOLIC STEROIDS: They are synthetic androgens with more anabolic and less androgenic activity (Table 8.7.1).

- They are responsible for enhanced protein synthesis and increase muscle mass.
- With higher doses, the relative anabolic activity is lost.
- Adverse effects are similar to those caused by androgens.

Table 8.7.1: Preparations of anabolic steroids

Anabolic steroid	Route	Dose	Trade name
Nandrolone phenylpropionate	IM	10-50 mg/ week	DURABOLIN
Nandrolone decanoate	IM	25-100 mg/ 3 weeks	DECADURABOLIN
Methandienone	Oral	2-10 mg/ day	PRONABOL
Ethylestrenol	Oral	2-4 mg/ day	ORABOLIN
Oxandrolone	Oral	5-10 mg/ day	ANAVAR
Stanozolone	Oral	2-10 mg/ day	STROMBA

Uses

Catabolic states: Anabolic steroids may benefit patients following surgery, trauma, and prolonged illness and certain debilitating conditions. Given during convalescence, the negative nitrogen balance is corrected. It improves appetite and there is a feeling of well-being.

Senile osteoporosis: Respond well

Growth stimulation in children: Anabolic steroids promote linear growth in prepubertal boys.

Abuse in athletes and sport person: It was a presumption that anabolic steroid improves athletic performance. When combined with adequate exercise, the muscle mass increases. But the dose used by athletes is very high and is associated with serious adverse effects.

Other uses: Anabolic steroids can be used in chronic renal failure (renal insufficiency) to reduce nitrogen load on the kidneys. It can also be used in conditions like hemolytic and malignancy associated anemia and to counteract steroid induced osteoporosis.

Contraindications for the use of Androgens

- Pregnancy
- Carcinoma of prostate/breast in males

- Infants and children
- Renal/cardiac and liver diseases.

ANTIANDROGENS

Antiandrogens: They are the substance or the chemicals which blocks the synthesis or the action of androgen. They can be used in treatment of acne, baldness, hypertrophy of carcinoma prostate and in precocious puberty in boys.

Inhibitors of testosterone synthesis

- Ketoconazole
- Leuprolide (GnRH and its analog)
- Spironolactone (K⁺ sparing diuretics)
- Finasteride and dutasteride: Alfa reductase inhibitor.

Androgen receptor antagonist

- *Flutamide and bicalutamide:* Nonsteroidal antiandrogen
- *Cyproterone acetate:* It is a progestin analog and has mild progestational activity.

Danazol: It is an ethisterone derivative and having mild anabolic, androgenic and progestational activity.

Flutamide: It is a potent competitive antagonist at androgen receptors. It is used with GnRH/leuprolide in the treatment of carcinoma prostate.

Cyproterone acetate

- Cyproterone acetate - a derivative of progesterone, competitively binds to androgen receptors and thus blocks the action of androgens.
- Cyproterone is used to treat severe hyper sexuality in males, in carcinoma prostate and in female hirsutism.

Finasteride: It inhibits the enzyme 5-alpha reductase and thus inhibits the conversion of testosterone to its active metabolite dihydrotestosterone which acts mainly in the male urogenital tract.

- Finasteride is used in **benign prostatic hypertrophy** to reduce the prostate size.
- Antifungal agents ketoconazole also inhibits steroid hormone synthesis and thereby inhibits androgen synthesis.

MALE CONTRACEPTIVES. The requirement of a safe and effective chemical contraceptive in men has not been fulfilled largely because it is difficult to totally suppress spermatogenesis. Various compounds including testosterone with progestin, estrogens with progestins, antiandrogens like cyproterone acetate have been tried, but are neither reliable nor safe.

- GnRH agonists and antagonists along with testosterone inhibit gonadotrophin secretion and it is being studied.
- **Gossypol**, a cotton seed derivative has shown to produce oligozoospermia and impair sperm motility in

Chinese studies. This effect is reversible in a few months. Hypokalemia is the major adverse effect.

DRUGS USED IN SEXUAL IMPOTENCE: Sexual impotence is the inability of a man to have satisfactory sexual intercourse due to inability to have and maintain an erection. Very often it is psychological while in some cases there could be an organic cause.

Several drugs have been tried including testosterone, yohimbine, papaverine and antidepressants. The recent introduction of **Sildenafil** (Viagra) has been a success in a large percentage of them.

Sildenafil (Viagra): Sildenafil inhibits the enzyme phosphodiesterase in the penis and thus prolongs the life of cyclic GMP. This causes relaxation of smooth muscle in

the corpus cavernosum and vasodilatation – both resulting in cavernosal engorgement and leads to penile erection.

- Sildenafil is given orally (50-100 mg) 1 hour before sexual activity.

Adverse effects and precautions

- Due to vasodilatation – headache, dizziness and nasal stuffiness can occur.
- It potentiates the hypotensive action of nitrates and is contraindicated in patients on nitrates and in patients with coronary artery disease. Elderly men above 60 years need less dose (25 mg).
- Patients with liver disease, kidney disease, bleeding disorders and elderly people are at a higher risk of toxicity. Several deaths have been reported in such patients.



S E C T I O N

9

Drugs Acting on Uterus

Uterine Stimulants

DEFINITION

Drugs which stimulate the uterine contractions are called *oxytocics* or *ecbolics*.

Oxytocics: These drugs stimulate uterine contractions, promote expulsion of fetus, prevent postpartum hemorrhage, help in the involution of uterus and facilitate expulsion of milk from the mammary glands during lactation. They include oxytocin, ergometrine, methyl ergometrine, prostaglandins-PGF₂α, PGE₂, misoprostol and quinine.

OXYTOCIN

Oxytocin is a peptide hormone secreted by the posterior pituitary along with ADH. It is synthesized in the Supra-optic and paraventricular nuclei of the hypothalamus, transported along the axon and stored in the neurohypophysis (posterior pituitary). It is released by stimuli such as suckling, coitus and parturition.

Actions: Uterus Oxytocin contracts the uterus. It stimulates pregnant and non-pregnant uterus, but the sensitivity of the uterus to oxytocin increases as the pregnancy advances, reaching a maximum at term. The fundus and the body contract, while the lower segment is relaxed. Both force and frequency of contractions are enhanced and there is full relaxation in between the contraction. At full term, the uterus is highly sensitive to the effects of oxytocin as there is an increase in the number of oxytocin receptors.

- **Mammary gland:** Oxytocin facilitates milk ejection by contraction of the myoepithelium in the mammary alveoli. Suckling stimulates the release of oxytocin.
- It appears to function as peptide neurotransmitter in brain (CNS).
- It is inactive orally and is usually given IV or can also be given as nasal spray.

Uses: It is used for induction of labor. Oxytocin is used to induce or augment labor when contraction are inadequate, even at full-term of pregnancy.

1. **PPH:** As an alternative to ergometrine.
2. **Milk ejection:** When ejection is impaired in nursing mothers, intranasal spray can be used.
3. **Abortion:** As an alternative to induce midtrimester abortion.
4. **Breast engorgement.**

Adverse effects: Large doses cause water intoxication and very powerful contractions of the Uterus, and may lead to soft tissue injury or Uterine rupture.

ERGOMETRINE AND METHYL ERGOMETRINE

Ergometrine is an alkaloid obtained from ergot, while methyl-ergometrine is semi synthetic. Both are active orally, have a rapid onset of effect and are devoid of adrenergic blocking and vasoconstrictor effect present in other ergot alkaloids, viz., ergotoxine, ergotamine and DHE.

Actions: Uterus : Ergometrine is a powerful uterine stimulant. The force and frequency of uterine contractions are enhanced; lower segment also contracts. There is no relaxation in between contraction. Ergometrine stimulates the uterus during all phases of gestation, but the uterus at full-term and immediately after delivery is highly sensitive to its effects.

It has no effect on the mammary gland.

Uses: They are completely absorbed if given orally onset of action—oral – 15 min. IM – 15 min and IV – immediate.

1. **Postpartum hemorrhage** – Ergometrine is used to treat and prevent PPH (Postpartum hemorrhage)
2. **To hasten uterine involution** – Ergometrine is given for 7 days.
3. **To prevent uterine atony** – After cesarean section.

Adverse effects: Adverse effects include nausea, vomiting and rarely hypertension.

PROSTAGLANDINS

- PGE_2 and $\text{PGF}_2\alpha$ stimulate the contraction for both pregnant and non-pregnant uterus though sensitivity is higher during pregnancy.
- They also soften the cervix and hasten dilatation (cervical ripening). PGs produced by fetal tissues mediate initiation and progression of labor.

Uses: It is used for following purpose:

1. *Abortion:* PGs are used as vaginal suppositories to induce midtrimester abortion. They are also used with mifepristone in termination of pregnancy up to 9 weeks.
2. *PPH:* As an alternative to ergometrine.
3. *Cervical priming:* Gels are used intravaginally to soften the cervix.
4. *Induction of labor:* PGs are used as alternatives to oxytocin.

Adverse effects: They include : nausea, vomiting, headache, fever and diarrhea.

Uterine Relaxants (Tocolytic Agents)

DEFINITION

These drugs cause relaxation of uterus and are used for the management of premature labor and to stop labor temporarily in order to prepare the patient for more complicated delivery. Tocolytics reduce uterine motility. They are:

- β_2 -adrenergic agonists like salbutamol, terbutaline and isoxuprine.
- *Miscellaneous*-ethylalcohol, calcium channel blockers, aspirin, magnesium sulfate, etc.
- **Intravenous magnesium sulfate:** It is used as an alternative when agonists are contraindicated. But high doses can cause significant CNS and respiratory depression, and cardiac arrhythmias.
- **Adrenergic agonists:** Ritodrine is a selective β_2 agonist. It is a powerful tocolytic agent and used to suppress premature labor and to delay delivery in some important circumstances. It postponed the delivery in approx 75% of the cases by about few hours to few days.

It was found to increase maternal mortality. It should not be administered if the mother is diabetic, cardiac problem and receiving β blockers or steroid. In neonates it may cause hypoglycemia and ileus. salbutamol and terbutalines are the alternative.

- **Calcium channel blockers** like nifedipine relaxes the uterus but can reduce placental perfusion and hence are not preferred. Alcohol given IV is a tocolytic but produces marked CNS depression. Similarly aspirin is not preferred as a tocolytic because of the risk of closure of ductus arteriosus and other adverse effects.

Uses of Tocolytics

1. To delay premature labor.
2. PG synthesis inhibitors-naproxen, indomethacin.
3. In threatened abortion to inhibit uterine contractions and in.
4. Dysmenorrhea.



S E C T I O N

10

Gastrointestinal System

Dyspepsia, Peptic Ulcers and their Management

DYSPEPSIA

Definition: It is a common symptom reflecting GIT disturbance (Fig. 10.1.1). Patient complains of vague feeling of discomfort in upper abdomen. There may be pain or burning sensation, feeling of fullness of the abdomen (usually described by the patient as collection of the gases in the stomach- flatulent dyspepsia), There may be belching and eructation. Patient may feel relief after belching. Dyspepsia may be because of irritation of the stomach by the disease process or by administration of the drugs. It may also be because of collection of gases because of habit of air-swallowing (aerophagy). There may be hypersecretion of gastric acid.

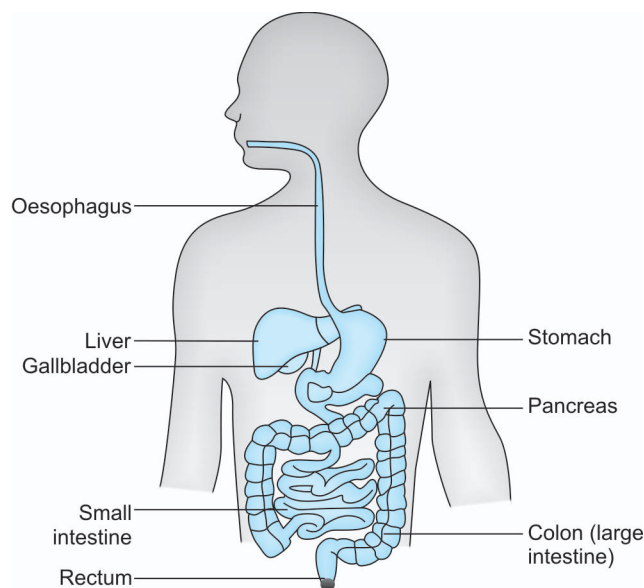


Fig. 10.1.1: The digestive system

Treatment of Dyspepsia

Drugs provide symptomatic relief. Following drugs may bring some benefit:

Carminatives:

- These are the substances that cause mild stimulation of the gastrointestinal tract and cause relaxation of the sphincters. When sphincter at the cardiac end of the stomach relaxes, the gases escape through the esophagus and patient feels relief. Antispasmodic action may also be helpful to relieve the pain due to spasm. Carminatives give some sensation of warmth and that is liked by the patient.
- Cinnamon, cardamom, ginger, cumin seeds, caraway, dill, pepper, asafoetida, are the examples of the substances having carminative property. Almost all these substances are used in Indian kitchen. They are described as condiments or spices. Mint and CO₂ also have carminative action.
- **Carminative mixture:** A compounded preparation is having the following formulation:

Sodium bicarbonate	1 g
Tincture cardamom compound	2 ml
Simple Syrup	2 ml
Water up to	30 ml

This mixture is usually prescribed after meals. 30 ml is the dose which is repeated three times a day. If given before meals, it may serve as appetizer.

Other carminatives available:

- **Dimethicone:** Tab 25 mg
- **Methylpolysiloxane:** 25 mg/10 ml.

Digestive Enzyme Preparations

- Amylase, trypsin, lipase (pancreatin), diastase, etc.
- These will help ONLY if there is deficiency of these enzymes. It is NOT very common or is not the cause of dyspepsia in all cases.

Adsorbents and Defoaming Agents

- Activated charcoal adsorbs the gases. Simethicone acts as surface tension reducing agent (result in collapsing of small air bubbles).
- These compounds may have value as an adjuvant.

Antacids and Agents Reducing Acid Secretion

- These agents will be helpful if increased gastric acid secretion is the cause of dyspepsia.

Prokinetic Agents

- These agents will increase gastric motility and would hurry the passage of food from stomach onwards. If gastric stasis (e.g. diabetic gastro-paresis) is the reason for dyspepsia these agents would be useful.

PEPTIC ULCER

- Acid-peptic disease is common in the present days that are full of tension and anxiety. Peptic ulcer may result from increased acid secretion or impaired defense mechanism of gastric mucosa or both (see Fig. 10.1.2).

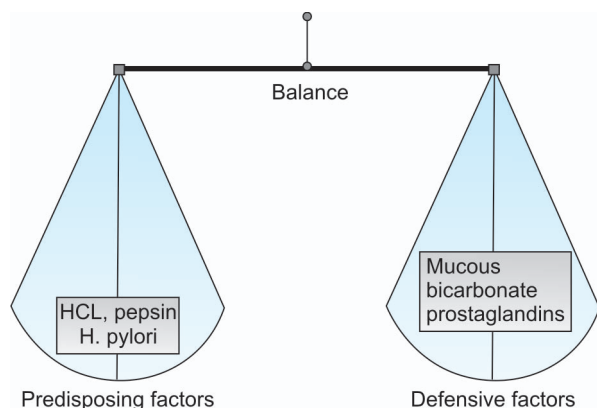


Fig. 10.1.2: Balance between predisposing factors and defensive factors

- It is thought to result from an imbalance between acid-pepsin secretion and mucosal, bicarbonate and prostaglandins (Fig. 10.1.2).
- Gastric acid secretion is regulated by three pathways—vagus (ACh), gastrin and local release of histamine—each acting through its own receptors. These activate $H^+ K^+$ ATPase (proton pump) on the parietal cells resulting in the secretion of H^+ into the gastric lumen where it combines with Cl^- (drawn from plasma) and HCl is secreted (Fig. 10.1.3).
- Acetylcholine and gastrin act both directly on the parietal cells and indirectly by releasing histamine from the enterochromaffin cells.

- Histamine acts through H_2 receptors on the parietal cells while acetylcholine through M_1 muscarinic and gastrin through G receptors (Fig. 10.1.3).
- AIM of the treatment should be to control the pain, to help in healing of the ulcer and to prevent complications like bleeding and perforation and prevent relapse.

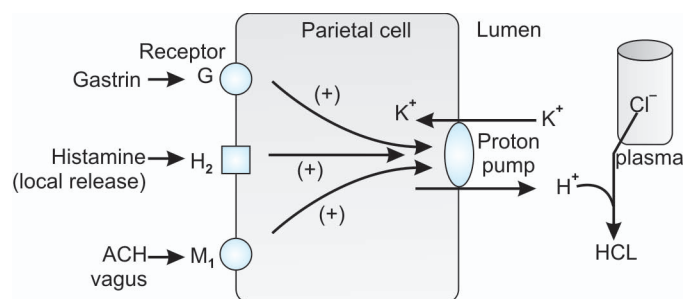


Fig. 10.1.3: Synthesis of HCL

Classification

- Drugs that neutralize gastric acid Antacids; $Al(OH)_3$, $Mg(OH)_2$.
- Drugs that reduce gastric acid secretion.
 - H_2 receptor blockers – Cimetidine, Ranitidine, Famotidine, Roxatidine, Nizatidine.
 - Proton pump inhibitors – Omeprazole, Lansoprazole, Pantoprazole
 - Muscarinic antagonists – Pirenzepine.
- Ulcer protectives: Sucralfate, Bismuth compounds.
- Other drugs: Carbenoxolone, Prostaglandin (analogues, i.e. misoprostole).
- Anti H. Pylori drugs.

ANTACIDS

- Antacids are basic substances which when given orally, neutralizes the gastric acid and raise the pH of gastric contents. Peptic activity is also reduced, as pepsin is active only above pH 4.
- Antacids are of 2 types:
 - Systemic: Sodium bicarbonate
 - Nonsystemic: Aluminium hydroxide, Magnesium trisilicate, Magnesium hydroxide, Calcium carbonate.

Systemic Antacids

- Sodium bicarbonate is rapid but short-acting. CO_2 that is released in the stomach escapes as eructation.
- It gets absorbed from the intestines leading to systemic alkalosis. There is 'rebound' hyperacidity as gastrin levels increases due to raised gastric pH. Sodium load may increase.
- It is not preferred because of the above disadvantages.
- Sodium bicarbonate is used with other antacids in peptic ulcer. Other uses are to alkalinise the urine in poisoning and to treat metabolic acidosis.

Non-systemic Antacids

- Non-systemic antacids are insoluble compounds that react in the stomach with HCl to form a chloride salt and water. They are not absorbed.
- **Aluminium hydroxide** $[\text{Al}(\text{OH})_3]$ is slow acting. Food further slows its neutralizing capacity. It is also an astringent and demulcent – forms a protective coating over the ulcers.
- The aluminium ions relax the smooth muscles resulting in delayed gastric emptying and constipation. Aluminium hydroxide binds phosphate and prevents its absorption resulting in hypophosphatemia on prolonged use.
- **Magnesium salts** $[\text{Mg}(\text{OH})_2]$ The action is quick and prolonged. Rebound acidity is mild.
- Magnesium salts are osmotic purgatives and the dose used as antacids may cause mild diarrhea.
- **Calcium carbonate** (CaCO_3) acts quickly and has prolonged action but liberates CO_2 which may cause discomfort. It may also cause constipation and hypercalcemia.

Antacid combinations are given to obtain maximum effects with least adverse effects as follows:

1. Quick and prolonged effect – Fast-acting $[\text{Mg}(\text{OH})_2]$ and slow acting $[\text{Al}(\text{OH})_3]$ are combined.
2. Neutralising side effects – Magnesium salts have a laxative effect while aluminium salts are constipating-combination neutralizes each others side effects.
3. Gastric emptying – Magnesium salts hasten while aluminium salts delay gastric emptying.

Note: All antacid tablets should be chewed and swallowed with 2 glasses of water as they do not disintegrate well in the stomach. Gels are more effective than tablets. One dose given 1 hr after food neutralizes the acid. (for 2 hours)

As per according to katzung basic and chemical pharmacology, 10th edition antacid also promotes mucosal defence mechanisms through stimulation of mucosal prostaglandin production.

Uses: Antacids are used as adjuvant in hyperacidity, peptic ulcer and reflux esophagitis.

Drug interactions

- Antacids form complexes with iron, tetracyclines, digoxin, ranitidine, fluoroquinolones, sulfonamides and antimuscarinic drugs.
- To avoid these, antacids should be taken 2 hours before or 2 hours after other drugs.

H₂ RECEPTOR BLOCKERS

- Cimetidine, ranitidine, famotidine, roxatidine.

- These drugs competitively inhibit the action of histamine on H₂ receptors and thereby reduce gastric secretion. Both volume and acidity of basal, nocturnal and food induced secretion are reduced.
- They can cause 90% reduction in gastric secretion by a single dose. Gastrin induced HCl secretion and pepsin is also reduced. These actions hasten the healing of peptic ulcers.
- Pharmacokinetics: H₂ blockers are well-absorbed. Cimetidine acts for 5-8 hours, ranitidine and famotidine for 12 hours.

Adverse effects: The H₂ blockers are well-tolerated. Their adverse effects are discussed with individual agents.

Cimetidine

- It has antiandrogenic actions, it increases plasma prolactin levels and inhibits estrogen metabolism in the liver.
- Headache, dizziness, rashes and diarrhea can result.
- On prolonged use it may result in gynecomastia, impotence and loss of libido.
- CNS effects include confusion, delirium and hallucinations in the elderly.
- Cimetidine inhibits microsomal enzymes and interferes with the metabolism of many drugs.

Ranitidine

- It is the preferred H₂ blocker as it has several advantages over cimetidine.
- Ranitidine is more potent, longer acting, has no antiandrogenic effects, no CNS effects as it does not cross BBB and does not inhibit microsomal enzymes significantly.
- Only adverse effects are headache and dizziness.

Famotidine

- It is similar to but more potent than ranitidine.
- Headache and rashes can occur.
- More suitable for ZE syndrome.

Roxatidine. It is similar to ranitidine but is more potent and longer-acting.

Loxatidine. Newer drug. Completely block HCl secretion.

Uses of H₂ blockers

- H₂ blockers are used in the treatment of peptic ulcer, gastritis, reflux esophagitis, and as preanesthetic medication and to prevent damage if aspiration pneumonia occurs during surgery.
- Ranitidine is the most preferred. It is given for 4-8 weeks in peptic ulcers. It may be continued for 6 months to prevent recurrence.

PROTON PUMP INHIBITORS

Omeprazole

- The parietal cells of the stomach secrete H^+ with the help of an enzyme $H^+ K^+$ ATPase (proton pump) present in the plasma membrane.
- This is the final step in gastric acid secretion due to any stimuli. Proton pump inhibitors specifically inhibit this enzyme and thereby inhibit gastric secretion.
- Omeprazole is a prodrug, gets activated in the acidic environment of the stomach and a single dose can totally inhibit gastric secretion.
- Acid secretion starts only after new $H^+ K^+$ ATPase enzyme is synthesized. Ulcer heals rapidly even in resistant cases.

Uses

- Omeprazole is used in peptic ulcers and severe gastroesophageal reflux diseases that is not responding to H_2 blockers. (GERD)
- Zollinger - Ellison (ZE) syndroms.
- Ulcers heal fast and pain is relieved. It is given for 4-8 weeks.
- It also inhibits the growth of *H. Pylori*, directly and by $\uparrow$ PH.

Adverse effects

- Omeprazole is well-tolerated.
- Prolonged acid suppression may allow bacterial overgrowth in the stomach. Carcinoid tumors are reported in rats but not in humans.
- Dizziness, headache, nausea and rashes are rare.

Lansoprazole: It is similar to omeprazole but is longer-acting.

- Pantoprazole, Rabeprazole and Esmoprazole are the newer agents.

Anticholinergics

- Though atropine reduces gastric secretion, the dose needed results in several adverse effects.
- A derivative of atropine—pirenzepine selectively blocks gastric M_1 receptors and inhibits gastric secretion by 40-50% without significant side effects.
- It also inhibits the secretion of gastrin, mucous and bicarbonate. It is used as an adjuvant.

ULCER PROTECTIVES (Table 10.1.1)

Sucralfate

- In acidic medium (pH < 4), sucralfate polymerizes to form a sticky, viscid gel which firmly adheres to the base of the ulcers.
- It remains there for over 6 hours acting as a physical barrier and prevents contact of mucosa and submucosa with acid and pepsin.

Table 10.1.1: Dosage and frequency of administration of drugs used in peptic ulcer

Drug	Dose and frequency
Cimetidine	400 mg BD/800 mg HS
Ranitidine	150-BD/300 mg HS
Famotidine	20 mg BD/40 mg HS
Roxatidine	75 mg BD/150 mg HS
Omeprazole	20-40 mg OD
Lansoprazole	15-30 mg OD
Sucralfate (SUCRACE)	1 g 1 hr before each meal
Colloidal bismuth sub-citrate	120 mg 1 hr before meals and at bed time
Carbenoxolone	50-100 mg TDSs
Misoprostol	200 mg BD-QID

- It also stimulates the PG synthesis in gastric mucosa. It thus promotes healing by protecting the ulcer. Sucralfate is not absorbed and is well-tolerated.
- One tablet is given 1 hr before each meal and one at bed time for 4-8 weeks and then 1 gram BD is continued for 6 months to prevent recurrence.
- Side effects are rare and include constipation and dryness of mouth.

Drug interactions

- Sucralfate needs acidic pH for activation. **Hence ant-acids should not be given with it.**
- Sucralfate absorbs and interferes with the absorption of tetracyclines, digoxin, phenytoin and cimetidine.

Bismuth salts

- Colloidal bismuth sub-citrate on oral administration chelate proteins in the ulcer base and forms a protective coating over the gastric mucosa.
- It also inhibits the growth of *H. pylori* on gastric mucosa and stimulates the mucous production and PG synthesis.
- By these actions it promotes ulcer healing in 4-8 weeks. It may cause constipation and black stools.

OTHER DRUGS

Carbenoxolone

- It is a steroid like compound obtained from glycyrrhizic acid found in the root of liquorice.
- On ingestion, it alters the composition of mucous so that it is more viscid and adheres to gastric mucosa to protect the ulcer base.
- It also inhibits pepsin activity and prolongs the life of PGs. Because of its steroid like effects, it causes salt and water retention. *It is therefore not preferred.*

Prostaglandin analogues

- PGE_2 and PGI_2 synthesized by the gastric mucosa inhibits gastric secretion, enhances mucous production and exerts a cytoprotective effect.
- PG analogs **misoprostol and enprostil** given orally are of special value in preventing drug induced (e.g. NSAIDs) gastric ulceration. Diarrhea and muscle cramps are common.

Treatment of H. pylori Infection

- The gram negative bacterium H. pylori is adapted to living in the stomach.
- Infection with H. pylori is associated with gastroduodenal disease including gastritis and peptic ulcer. It is also thought to be responsible for recurrence of peptic ulcer disease.
- Eradication of H. pylori along with drugs that reduce acid secretion has shown to reduce the relapse rate.

Various combination regimens are tried with clarithromycin, amoxicillin or tetracycline; metronidazole and omeprazole for 1-2 weeks.

Other drugs: For eradication H. pylori : Metronidazole, Tetracycline, Amoxicillin, etc.

Triple drug regimen is preferred:

- Colloidal bismuth subcitrate 120 mg qid + Tetracycline 500 mg qid/Amoxicillin 500 mg tid + Metronidazole 400 mg tid (all for 14 days). Other options are:
- Omeprazole 20 mg bid + Clarithromycin 500 mg bid + Amoxicillin 1 g bid (all for 7 days);
- (ii) Ranitidine 300 mg OD + Amoxicillin 750 mg tid + Metronidazole 500 mg tid x 12 days.

General Measures:

1. Diet: regular, frequent and nutritious.
2. Food: Avoid any precipitating substance.
3. Milk: relieve pain.
4. Tea/Coffee/Juices: Take in moderate amount.
5. Avoid alcohol and smoking.
6. Avoid certain drugs like Aspirin
7. Adequate sleep and rest.

Abdominal Colic, Emetics and Antiemetics

ABDOMINAL COLIC

- Colicky pain in abdomen is usually acute in onset and may be very severe. Usually it is of intestinal origin (**intestinal colic**) resulting from severe spasms of intestinal smooth muscles.
- Gall bladder (**biliary colic**) or
- Urinary tract (**renal/ureteric colic**) may also contribute to such painful episodes.
- In infants, intestinal spasms are quite common and are referred to as infantile colic. It should be managed by proper feeding technique, changing posture, hot fomentation (avoid using antispasmodics).

Drugs for treatment of (Abdominal Colic): Aim is to relieve the spasm so that the patient may get comfort.

- Anticholinergics (atropine and atropine-substitutes) are commonly used as antispasmodics. These include: atropine, dicyclomine (a tertiary compound), oxyphenonium, propantheline, pipenzolate, poldine, (all quaternary compounds = less CNS action). Avoid using these agents in infants below the age of 6 months.
- Other agents include mebeverine, papaverine (both directly acting smooth muscle relaxants), dill oil and fennel oil (traditional remedies), simethicone (antiflatulent) etc.
- Analgesics of opioid type may be useful but are not preferred for intestinal colic.
- In renal colic, antispasmodics will be of help to reduce the pain. Opioid analgesics may also be needed in this situation to control the pain.
- Phenazopyridine is considered as urinary analgesic as it provides symptomatic relief from dysuria and burning sensation.
- Biliary tract spasm requires opioid analgesic and atropine or atropine like drug.

Atropine: Inj 0.6 mg/ml. Dose: Adults: 0.4-0.6 mg, [Children: 0.01 mg/kg/dose qid.]

Hyoscine butyl bromide: Tab 10 mg., Inj. 20 mg/ml/amp. Dose : 20 mg qid.

Dicyclomine: Tab 10-20 mg, Drops 10 mg/ml, Inj 20 mg/2 ml. Dose : Adults : 10-20 mg 3-4 per day; Children: 6 months-2 yrs → 5-10 mg tid, 2-12 yrs → 10 mg tid.

Oxyphenonium: Tab 5-10 mg. Dose: 5-10 mg qid orally.

Propantheline: Tab 15 mg. Dose: 15 mg tid orally.

Pipenzolate: Tab 5 mg, Drops 4 mg/ml. Dose: 8 mg tid orally.

EMETICS AND ANTIEMETICS

- Stimulation of the vomiting center in the medulla oblongata results in vomiting.
- The vomiting center receives afferents from the chemoreceptor trigger zone (CTZ), vestibular apparatus, GI tract and centers in the brain.
- CTZ is not protected by the blood-brain barrier and is stimulated by various drugs, chemicals and radiation.

EMETICS

Drugs which are used to induce vomiting are called emetics. When a noxious substance is ingested, vomiting has to be induced. Mustard powder (1 teaspoon with water) or hypertonic salt solution can evoke vomiting. Even on touching posterior pharyngeal wall with finger (gag reflex) can induce vomiting

- Apomorphine is a derivative of morphine. Given SC/IM, it produces vomiting in 5-10 minutes. It acts by stimulating the CTZ.
- Ipecacuanha contains an alkaloid emetine. Given as a syrup (15-20 ml), it produces vomiting in 15 minutes. It is safe even in children.

ANTIEMETICS (FIG. 10.2.1)

Vomiting is a protective mechanism aimed at eliminating the unwanted harmful material from the stomach. But in some situations, vomiting may not serve any useful purpose and may only be troublesome. In such circumstances, vomiting needs to be suppressed.

Nausea and vomiting may occur in various conditions. Causes may be broadly classified in to:

- *Gastrointestinal*: Indigestion, Gastroenteritis, intestinal obstruction or food intolerance;
- Administration of drugs (*Drug Induced Vomiting*) - through GI irritation or action on CTZ;
- Certain *systemic diseases*, e.g. hepatitis, meningitis, renal failure;
- *Pregnancy* – morning sickness (if very severe - hyperemesis gravidarum);
- During traveling - *motion sickness*; and
- Postoperative.

Classification of Antiemetic

1. Neuroleptics: Chlorpromazine, Prochlorperazine, Haloperidol.
2. Dopamine (D_2) antagonists: Prokinetics: Metoclopramide, Domperidone.
3. Antimuscarinics: Hyoscine (scopolamine)

4. H_1 antihistamines like: Meclozine, Cyclizine, Promethazine, Diphenhydramine.
5. $5HT_3$ antagonists: Ondansetron, Granisetron.
6. Other agents: Cisapride, Corticosteroids.

Neuroleptics

Phenothiazines: Chlorpromazine, prochlorperazine, trifluorpromazine.

- They have anti-dopaminergic (**D_2 receptors at - CTZ**), anti-cholinergic and anti-histaminic properties. They are potent anti-emetics and are effective in vomiting of almost all varieties (except motion sickness). As their side effects, they may produce extrapyramidal symptoms particularly when long-term treatment is given but acute dystonia may occur even with the first dose. Acute dystonia may be horrifying to the patient, the family members and to the physician also if he is not aware of it.
- *Acute dystonia* is treated by anticholinergic drugs (e.g. benzhexol, bethtropine) or antihistaminics (e.g. promethazine, hydroxyzine). Other extrapyramidal reactions include parkinsonism-like symptoms, akathisia and dyskinesia. Sedation and hypotension are the other important side effects. Phenothiazines are not recommended for children under 10 kg body weight as antiemetics.

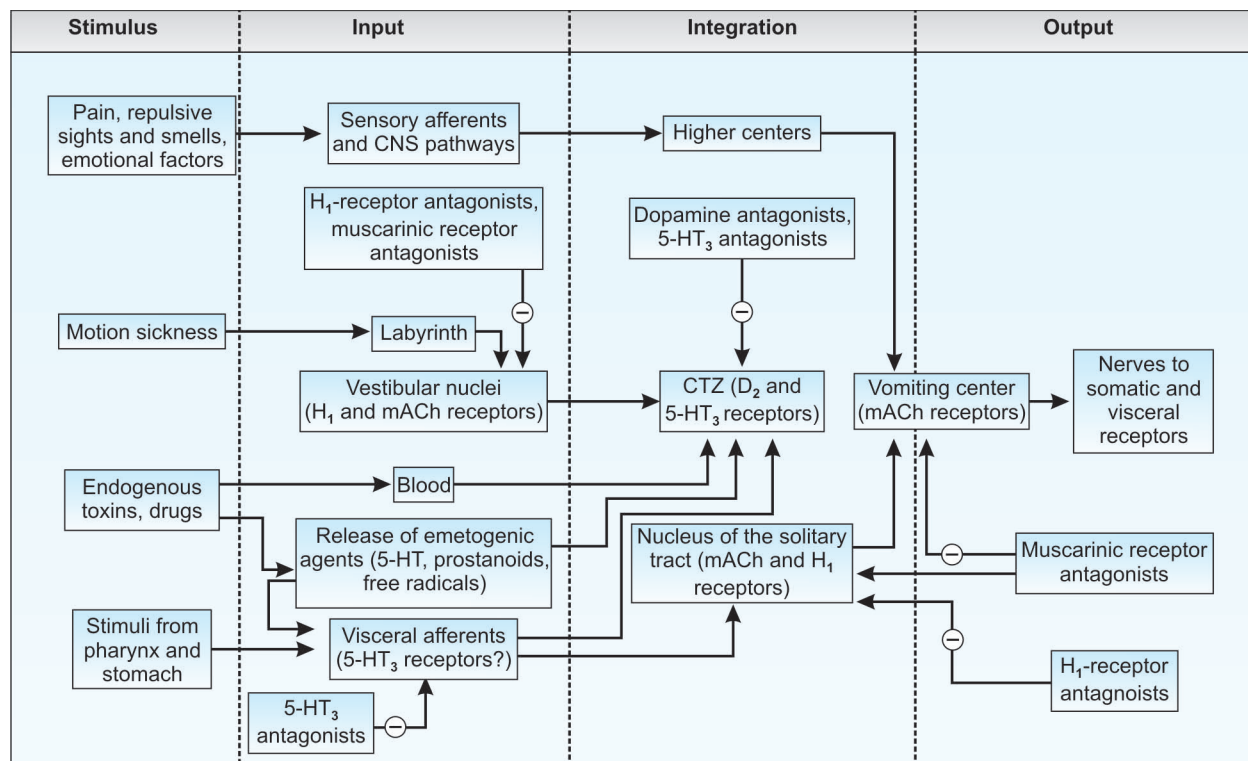


Fig. 10.2.1: Various stimuli, pathways and centers for emesis

Chlorpromazine: Tab 10-25-50-100-200 mg, Inj 25 mg/ml. Dose : 25 mg tid orally.

Triflupromazine: Tab 10 mg, Inj 10 mg/ml. Dose : 5-15 mg IM/PO tid.

Prochlorperazine: Tab 5-25 mg, Inj 12.5 mg/ml. Dose: 5-10 mg 3-4/day orally, 12.5 mg deep IM

(Other anti-psychotic like haloperidol can also be used as antiemetic)

Dopamine D₂ Antagonists

Prokinetics: Metoclopramide, Domperidone.

- Metoclopramide acts centrally by blocking dopamine D₂ receptors in the CTZ. It lowers the tone of the lower esophageal sphincter and enhances gastric peristalsis. It is used in nausea and vomiting due to gastrointestinal disorders, migraine, in postoperative period and vomiting due to cytotoxic drugs and radiotherapy.
- Domperidone acts like metoclopramide with fewer side effects.

[Both are discussed separately under heading prokinetic drugs]

Antimuscarinics

Hyoscine

- Hyoscine is also called as scopolamine. *It is a labyrinthine sedative which is very effective in motion sickness.*
- Motion sickness or traveling sickness** is due to over stimulation of vestibular apparatus along with psychological and environmental factors.
- Hyoscine (0.4-0.6 mg) should be taken orally, 30 minutes before journey, acts for 6 hours and the dose should be repeated if the journey is longer than that.
- A transdermal patch delivers hyoscine constantly over 3 days and is to be applied behind the ear.
- Sedation and dry mouth are common side effects.

H₁ antihistamines

- Promethazine, diphenhydramine, cyclizine and cinnarizine have anticholinergic properties.
- They probably act both centrally and on the GI tract.
- They are useful in motion sickness and postoperative vomiting.*

5-HT₃ Antagonists

Ondansetron

- 5-hydroxytryptamine released in the gut is an important transmitter of emesis. Ondansetron blocks 5-HT₃ receptors in the GI tract and CTZ and prevents vomiting.
- It is a powerful antiemetic and can be given orally or intravenously (4-8 mg). It is specially useful to control vomiting induced by anticancer drugs or radiotherapy.

- It is also useful in postoperative vomiting and other drugs induced vomiting.
- Adverse effects include headache and gastrointestinal upset.*

Granisetron: It is more potent than ondansetron as an antiemetic.

OTHER ANTIEMETICS

Corticosteroids: They are used as adjuvants with other antiemetics like ondansetron or metoclopramide.

Dicyclomine: It is used to control vomiting in morning sickness and motion sickness.

Nausea and Vomiting Associated With Pregnancy (Morning Sickness) (Table 10.2.1)

- Due to high levels of estrogen, threshold of the CTZ is decreased during first trimester of pregnancy.
- Gradually tolerance develops to estrogen and the condition subsides. Severe nausea and vomiting during pregnancy is called **hyperemesis gravidarum**.
- Management of 'morning sickness' comprises of : rest, assurance and dietary measures (frequent, high carbohydrate meals and more fluids).
- When morning sickness is severe enough to interfere with nutrition, drug treatment is indicated. *Pyridoxine may be tried first.*
- Selection of antiemetic drug may be made from (in order of preference): antihistaminic (e.g. meclizine, dimenhydrinate, promethazine) or metoclopramide or a phenothiazine derivative. Hyperemesis gravidarum requires fluid and electrolyte management also.

Table 10.2.1: Preferred drugs for vomiting due to various causes

Conditions	Drugs
Motion sickness	Hyoscine, Cyclizine, Promethazine, Cinnarizine
Vomiting in pregnancy	Ondansetron + Dexamethasone
Vomiting due to other drugs	Chlorpromazine, Metoclopramide
Postoperative vomiting	Ondansetron, Metoclopramide
Vomiting in pregnancy	Dicyclomine, Pyridoxine, Cyclizine, Meclizine, Metoclopramide

Prokinetic Agents

DEFINITION

Drugs that enhance (increase) gastroduodenal motility and hasten gastric emptying are called prokinetic agents. Metoclopramide, cisapride and domperidone are examples of prokinetic agents.

Metoclopramide

Actions

GIT : Metoclopramide promotes forward movement of contents of the upper GI tract. It raises lower esophageal sphincter pressure, speeds up gastric emptying, prevents reflux esophagitis and also slightly enhances intestinal peristalsis.

CNS : Metoclopramide acts as an antiemetic by its actions on CTZ and by speeding up gastric emptying.

Mechanism of action

Prokinetics act : by enhancing acetylcholine release (5HT₄ agonist) from the cholinergic neurons in the gut, ultimately increases peristaltic movement and therefore prokinetic action.

- Antiemetic action is due to blockade of D₂ receptors in the CTZ.

Adverse effects: They are sedation, dystonia and diarrhea, gynaecomastia, galactorrhea and parkinsonism (extrapyramidal symptoms) can occur on long-term use.

Uses

- *Reflux esophagitis* (GERD) – ‘heart burn’ due to reflux of acid into the esophagus is benefited by prokinetic agents.
- As *antiemetics* – in postoperative period and vomiting due to anticancer drugs.

- As *preanesthetic* medication to promote gastric emptying before induction of general anesthesia in emergency.
- In *endoscopy* – to assist passage of tubes into the duodenum.
- In *dyspepsia*.

Domperidone

- It is a D₂ dopamine receptor blocker like metoclopramide.
- It does not cross the blood-brain barrier and hence extrapyramidal side effects are rare. As CTZ is outside the BBB, it acts as an antiemetic. Side effects are rare and include headache, dryness of mouth, diarrhea and rashes.
- Domperidone can be used in place of metoclopramide. arrhythmia may develop on rapid IV administration.
- Arrhythmia may develop on rapid IV administration.

Cisapride

- It enhances gastric motility by promoting the release of acetylcholine in the gut wall.
- It does not block dopamine receptors—hence is not an antiemetic and there are no antidopaminergic side effects.
- It also promotes colonic motility which may result in diarrhea. It is used in reflux esophagitis.
- Due to its arrhythmic tendency (↑Q T_c interval) it is not used in various countries.

Gastroesophageal Reflux Disorder (GERD)

Definition: Reflux of acidic gastric contents into the esophagus results in ‘heart burn’ due to esophagitis. The condition is also called as **GERD (Gastroesophageal Reflux Disorder)**.

- Based on severity, it may be treated with antacids, metoclopramide or drugs that reduce acid secretion.
- **Omeprazole** is the most effective agent. Prolong therapy is required.
- H_2 blockers: Less HCl suppression than PPIs (omeproazole). No effect on LES.
- Antacids: Used for intermittent and occasional relief.
- Prokinetic drugs: Metoclopramide and other drugs $\uparrow$ LES tone and ultimately controls regurgitation.
- Sodium alginate : forms froathy layer and prevents acid pepsin contact with esophagus avoiding heavy meals, late night dinner, smoking and alcohol is very helpful.

Drugs for Constipation and Diarrhea

CONSTIPATION

Definition

Constipation is not a disease, but is a symptom complex that includes decreased frequency of defecation, hard consistency of stool, and difficulty in stool passage.

- Constipation may be **acute** or **chronic**.
- It may be **functional** (not associated with any disease or structural abnormality) e.g. sedentary habits, old age, low fiber diet, physiological states like pregnancy, etc. or
- It may be **organic** resulting from endocrine disorders (diabetes, hypothyroidism), diseases of nervous system, mechanical obstruction. It may be even congenital.
- **Drugs** like opioids, anticholinergics, etc. may also produce constipation.

Purgatives: Purgatives are drugs that promote defecation. They are also called **laxatives and cathartics**.

- Laxation is the evacuation of formed faecal material. Laxatives have milder action. Catharsis is the evacuation of the unformed, usually watery fecal material. Cathartics are more powerful evacuants.

Classification

1. **Bulk laxatives:** Bran, Plantago seeds, Agar, Methylcellulose, Ispaghula husk
2. **Fecal softeners:** Docusate sodium, Liquid paraffin (emolients)
3. **Osmotic purgatives:** Magnesium sulphate, Magnesium hydroxide, Sodium sulphate, Lactulose
4. **Stimulant purgatives:** Phenolphthalein, Bisacodyl, Castor oil, Anthraquinones—Cascara sagrada, Senna

Bulk Forming Laxatives

- Dietary natural fibers (cellulose and indigestible contents such as lignin) **Bran, Agar, Isapgol** (Psyllium - husk or seeds) etc., semisynthetic compounds like **Methylcellulose, Carboxymethyl-cellulose**, and synthetic—**Calcium polycarbophil**.

- Dietary fibre consists of cell walls and other parts of fruits and vegetable that are unabsorbable. Adding fiber to the diet is a safe and natural way of treating constipation in persons on low-fiber diet. **Bran** is the residue left when flour is made from cereals and contains 40% fiber.
- Fibers from grains and cereals increase stool bulk as well as shorten intestinal transit time while fibers from fruits and vegetables are more water soluble and produce more moist stool without affecting transit time. Bulk forming laxatives **act slowly** (onset: 1-3 days).
- They also bind with bile acids in the GIT preventing their reabsorption. Consequently, conversion of cholesterol to bile acids in the liver increases, this in turn reduces cholesterol (total and in LDL). Flatulence and borborygmi are common side effects. Carboxymethylcellulose and psyllium contain significant quantities of Na which may get absorbed.
- Cellulose binds with and interferes with absorption of several drugs like digitalis, salicylates, coumarin anticoagulants and nitrofurantoin. Intestinal obstruction and impaction are other major adverse effects. Plenty of water should therefore be taken. (These agents are some times used to soften the stools and avoid straining). **Adequate water intake should be stressed.**

Stool Softening Agents

1. Emolient/lubricant purgatives: Liquid paraffin

- It **softens** the fecal material and **lubricates** the passage and thereby facilitates evacuation of fecal material, may also interfere with absorption of water. Straining at stool is avoided and this is particularly important in patients with ischemic heart disease, hernia, fissure in ano, piles, after cataract surgery or in pregnant women and aged patients. Onset is delayed. Allergic reactions, leakage through anus, malabsorption of fat-soluble vitamins, lipoid pneumonia and paraffinoma are the adverse effects.

2. **Surfactants:** Docusate, poloxamers, dehydrocholate
- They act primarily as **stool-wetting** and **softening** agents, allowing mixing of water, liquids and other fecal material. Docusate sodium (dioctyl sodium sulphosuccinate) softens feces by lowering the surface tension of the intestinal contents which allows more water to be retained in the feces.
 - By altering intestinal permeability, they also increase net water and electrolyte secretions in the intestine.
 - Their efficacy as laxatives is less and potential for toxicity is significant (cramps, rashes, nausea, increased absorption and toxicity of drugs like phenolphthalein, liquid paraffin and quinidine).
 - *Docusate should not be combined with paraffin.*

Saline/Osmotic Laxatives or Purgatives

Osmotic purgatives

- They are solutes that are not absorbed in the intestine, osmotically retain water and increase the bulk of intestinal contents. They increase peristalsis to evacuate a fluid stool.
- Magnesium hydroxide, Sodium potassium tartrate (Rochelle's salt), Sodium phosphates, Magnesium sulfate, Milk of magnesia (Magnesium hydroxide), Magnesium citrate, Magnesium carbonate, Glycerin, Lactulose, Mannitol, Sorbitol and Polyethylene glycol. are some inorganic salts used as osmotic or saline purgatives.
- They are used to prepare the bowel before surgery and in food poisoning.
- By their **osmotic action** they retain water in the colon. Stool will be watery in consistency. Increased bulk stretches the intestinal wall initiating peristalsis.
- Onset of action is **quick**: 1-3 hrs. Hence they should be administered in the morning on empty stomach. Up to 20% of the salt may get absorbed: Magnesium toxicity can occur if there is renal insufficiency, Na salts cause water retention while phosphates can lead to hypocalcemia.
- Hypertonic solutions can even cause dehydration and electrolyte disturbance. Apart from acute functional constipation they can be used for emptying the bowel prior to surgery and radiographic procedures, as adjuncts to anthelmintic therapy for evacuation of intestinal parasites and in some instances of poisoning.
- Lactulose is a disaccharide which hydrolyses after reaching cecum. There the hydrolyzed sugars are fermented into acids which exert osmotic effect (after a long delay of 24-48 hrs). It is also useful in hepatic encephalopathy.

An example of compounded preparation: (Alba mixture) single dose

Magnesium sulfate 8.0 g
Magnesium carbonate 1.2 g

Peppermint water up to 30.0 ml.

To be taken with tumblerful of water on empty stomach early in the morning.

Irritant/Stimulant Purgatives:

Phenolphthalein, Bisacodyl, Senna, Cascara sagrada, Castor oil (after breaking into ricinoleic acid, which is irritant).

- They promote accumulation of water and electrolytes in the colon and stimulate intestinal motility.
- Phenolphthalein may get absorbed and is excreted in urine (color will turn pink if urine is alkaline).
- Castor oil acts within 1-6 hrs, while senna, phenolphthalein or bisacodyl produce laxation after 6-8 hrs.
- *Major adverse effects are fluid and electrolyte deficits, inflammatory reaction in colon, gastric irritation, allergic reactions and cramps.*

Others

i. Suppository:

- Rectal suppositories can be used for treatment of constipation (Glycerin, Bisacodyl) [or as a drug delivery method, e.g. aminophylline, indomethacin].
- It is a useful method for pediatric, geriatric and terminally ill patients.

ii. **Evacuant Enema:** Soap water, tap water (in adults only), mineral or vegetable oil, glycerin, docusate, bisacodyl, etc.

- They cause distention and initiate peristalsis which results in evacuation of bowel. There is also fragmentation of hard fecal mass and liquefaction or lubrication of the feces.
- Enema are indicated in cases of fecal impaction (as in chronic constipation), prior to surgery or radiography or during USG or during labor - for emptying the bowel.

Phenolphthalein: It an indicator, acts on the colon after 6 to 8 hours to produce soft, semi liquid stools with some gripping. it undergoes enterohepatic circulation which prolongs its actions. Allergic reactions including pink colored skin eruptions, other severe forms of allergy and colic limit it's use.

Bisacodyl: It is related to phenolphthalein is converted to active metabolite in the intestines. It can be given orally (5 mg) but usually is used as rectal suppositories (10 mg) which results in defecation in 15-30 minutes. It is safe except that prolonged use may cause local inflammation.

Castor oil: It is hydrolysed in the upper small intestine to ricinoleic acid, a local irritant that increases intestinal motility. It is a powerful and one of the oldest purgatives. Stool is semiliquid and is accompanied by gripping. It is not preferred now a days due to availability of better drugs.

Table 10.4.1: Choice of purgatives

Conditions	Preferred laxative
1. Functional constipation	Increasing dietary fiber and adequate fluid intake.
2. Elderly patients	Increasing dietary fiber and adequate fluid intake.
3. Pregnancy	Dietary fiber.
4. To avoid straining at stools : as in hernia, piles, fissure, cardiovascular diseases like myocardial infarction	Bulk laxatives or fecal softeners
5. Irritable bowel syndrome: chronic constipation	Bulk laxatives
6. Food or drug poisoning	Osmotic purgatives
7. Bowel preparation before surgery, endoscopy and radiological examination	Bisacodyl, osmotic purgatives

Use of laxatives in constipation: Fiber rich diet, adequate fluid intake and physical activity are the best measures to prevent and treat constipation in the otherwise normal subjects. If these measures are inadequate, a laxative may be given.

Dangers of laxatives: They are not free from adverse effects. Non-pharmacological measures are often quite effective for prevention and treatment of constipation. If these are inadequate, then bulk forming agents should be used first. Stimulant laxatives should be used only in refractory cases. Prolonged and habitual use is unhealthy. They can even produce psychological dependence. Combinations of several laxatives have no advantage over single agents. Indeed, the combinations may be dangerous. Misconception about frequency, quantity and consistency of stools should be removed. Normal bowel movement may not return for several days after the use of higher doses of a purgative for a few days. Purgatives should **NOT** be used in patients with undiagnosed acute abdomen. Choice of purgatives are given in Table 10.4.1.

Note

- WHO Essential Drugs List includes only **Senna** as a laxative.
- National Essential Drugs List includes **Bisacodyl, Isapgol and Senna**

DRUGS USED IN THE TREATMENT OF DIARRHEA

Definition

- Diarrhea is the frequent passage of liquid stools. It can be due to a variety of causes like infection, toxins, anxiety and drugs.

- Acute diarrhea is one of the major causes of death in infants specially in the developing countries.
- In diarrhea, there is an increase in motility and secretions in the gut with depletion of water and electrolytes. Hence the approaches in the treatment of diarrhea include:
 1. replacement of fluid and electrolytes
 2. treatment of the cause
 3. antidiarrheal agents.
- Correction of fluid and electrolyte disturbances by oral rehydration with sodium chloride, glucose and water is useful and can be life saving in most cases especially in infants. This is called ORT (oral rehydration therapy).
- In the ileum, glucose enhances sodium absorption and water follows. Oral rehydration powders are available to be mixed with water for mild to moderate cases of dehydration.
- In severe degrees of dehydration, prompt intravenous rehydration is vital.

Composition of oral rehydration salt/solution (ORS): as per according to WHO

NaCl	3.5 gm
KCl	1.5 gm
Sodium citrate	2.9 gm
Glucose	20 gm

To be dissolved in 1 liter of boiled and cooled water. It can also be dissolved in 1 L. of clean drinking water.

- ORS should be taken at frequent interval, i.e. at 1/2 hrs. intervals or on demand (thirst).
- SUPER ORS or Modified ORS: → modified for improving the effectiveness of ORS.
- 1. By adding amino acid in ORS. (QUICK SOL PLUS) ↑ sodium absorption.
- 2. By adding rice into ORS (RICELYT Sachet) without glucose.

Treatment of the etiology

- Acute diarrhea could be due to bacterial, viral, or protozoal infection. The pathogen should be identified whenever possible and treated accordingly.
- Antidiarrheal drugs afford symptomatic relief and include adsorbents and antimotility drugs.
- Adsorbents include kaolin, pectin, chalk and activated charcoal. These adsorb intestinal toxins and microorganisms by coating it.

Antimotility Drugs

Codeine

- It is an opium alkaloid, stimulates the opioid receptors on the gastrointestinal smooth muscles to reduce peristalsis.
- This delays passage of intestinal contents and facilitates absorption of water.

- Nausea and vomiting may occur.
- Should not be used in ulcerative colitis like condition.

Diphenoxylate (LOMOTIL)

- It is an opioid related to pethidine.
- It is given with small dose of atropine in order to discourage abuse. In therapeutic doses CNS effects are not prominent and is used only in diarrheas.
- Nausea, drowsiness and abdominal pain may occur.

Loperamide (IMODIUM)

- It is an opiate.
- It has selective action on GI tract with additional antisecretory action. CNS effects are negligible.
- It is less sedating, less addicting and is the most commonly used antimotility drug.
- Its low solubility in water discourages abuse by injection.
- Loperamide may cause nausea, vomiting and abdominal cramps.
- It is contraindicated in children < 8 years.

Antimotility drugs—some preparations and dosage

Drugs	Trade names	Doses
Diphenoxylate 2.5 mg Atropine 0.025 mg	LOMOTIL	2-4 tablets stat; 1 every 6 hour
Loperamide	LOPESTAL	4 mg stat; 2 mg every 6 hour

Antimotility drugs are used for symptomatic treatment of non-infective diarrheas and traveller's diarrhea (as adjuvant).

Other drugs and diarrheal diseases

Lactobacillus acidophilus

- It is available as powders and tablets and is useful in some diarrheas.
- It promotes the growth of saccharolytic flora and alters the gut pH, so that growth of pathogenic organisms is inhibited.

Antispasmodics

- Atropine derivatives like propantheline and dicyclomine relax gastrointestinal smooth muscles and relieve abdominal colic's.

Inflammatory bowel diseases

- It can be due to ulcerative colitis or Crohn's disease.
- Like ulcerative colitis are treated with corticosteroids and sulphasalazine or mesalamine (mesalazine).
- These drugs are having anti-inflammatory action.
- It is not an infection disease therefore, anti-microbial agents have no role in controlling this disease.

Irritable bowel syndrome

- It is a common condition characterized by abnormal bowel functions with no specific organic cause.
- Diarrhea or constipation with abdominal pain are seen. Causes could be stress, lack of dietary fiber, food allergy or emotional disturbances.
- When constipation is prominent, soluble dietary fiber like ispaghula is recommended and loperamide is preferred for diarrhea.
- Benzodiazepines are given for the treatment of anxiety and other appropriate measures are taken depending on the symptoms and probable cause.

Traveller's diarrhea

- Infection is the most common cause of traveller's diarrhea and should be treated with suitable antimicrobials. It occurs in travellers who take unhygienic food, drinks and water.
- Oral rehydration salts and loperamide may also be used.
- Bismuth subsalicylate (tab DENOL) is used. It is an anti-inflammatory drug of Lieberkuhn.

Nutrition

- Starvation in patient of diarrhea is dangerous, start light balanced diet, e.g. rice, banana, smashed potato, cereals, etc. to fasten the recovery.

Antimicrobials in Diarrhea

- They are helpful only in acute infection diarrhea.
- Antimicrobials commonly used are.
 - Tetracycline (Cholera)
 - Fluoroquinolones. (Ciprofloxacin, Norfloxacin)
 - Shigella, C. jejuni
 - Metronidazole and Diloxinide fluorate—Entamoeba histolytica
 - Metronidazole—Giardia.
 - Metronidazole/Vancomycin—Cl. difficile



S E C T I O N

11

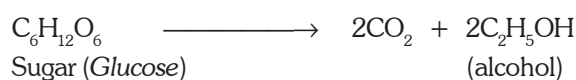
Central Nervous System

Alcohol

ALCOHOL

Alcohol is a substance which is not much important for its therapeutic use but extremely important for its worldwide use/abuse and a lot of controversies.

- Used since ancient time.
- Alcohols are the hydroxy derivatives of aliphatic hydrocarbons, i.e.
 - CH_3OH : Methyl alcohol
 - $\text{C}_2\text{H}_5\text{OH}$: Ethyl alcohol
- Production of alcohols require sugar, water, yeast, and warm atmosphere.
- Ethyl alcohol (alcohol in general) is a mono-hydroxy alcohol manufactured by fermentation of sugars (any high carbohydrate content substance, i.e. grapes, grains, etc.)



- It is a colorless, volatile, inflammable liquid. The ethanol content of various alcoholic beverages ranges from 4-55%.
- For industrial use: It is chiefly manufactured by organic synthesis from **ethylene**.

Ethanol (Ethyl Alcohol)

- It has limited therapeutic value
- Alcohol abuse (chronic alcoholism) and major socio-economics are the major diseases (not intoxication).
- Alcohol drinkers can be divided into:
 - a. Social drinkers
 - b. Social heavy drinkers (about 50% intoxicated)
 - c. Alcoholics (habitual drinkers)

BEVERAGE: Liquor for drinking

- Absolute alcohol: 99% w/w ethanol (dehydrated alcohol)

- Rectified spirit: 90% w/w ethanol
- Proof spirit: Old term, [gun powder + whisky] ignited
 - Explodes: Proof strength
 - If not explodes: water is present (diluted)
- 100% proof spirit: 49.29% v/v or 57.1% w/w alcohol.
- **Wines**
 - a. Light wines: (9–12% alcohol)—Claret, Cider, etc.
 - b. Fortified wines: (16–22% alcohol)—Distilled alcohol added port and sherry.
 - c. Effervescent wines: (12–16% alcohol)—Champagne [bottled before complete fermentation]
- **Spirit**: Distilled after fermentation, i.e. Rum, Gin, Whisky, Brandy, Vodka, etc.
- Blood alcohol concentration and clinical effect

50-100 mg/dL	: Sedation, Euphoria, increased retention time
100-200 mg/dL	: Ataxia/impaired motor functions, slurred speech impaired short term memory.
200-300 mg/dL	: Emesis/Staper
200-400 mg/dL	: Coma
> 500 mg/dL	: Respiratory depression and death
- In USA Adult blood level of 80–100 mg/dL, permitted for driving. (See Fig. 11.1.1)

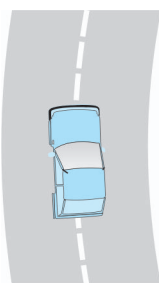
Pharmacokinetics

- Alcohol ($\text{C}_2\text{H}_5\text{OH}$), is water soluble and is rapidly/completely absorbed (80% from the small intestine).
- Absorption increases in empty stomach, while decreases with food and with other factors.
- After drinking, it can be detected in blood within 5 minutes.
- Its maximum absorption occurs within 30 to 60 minutes. Time varies from person to person.

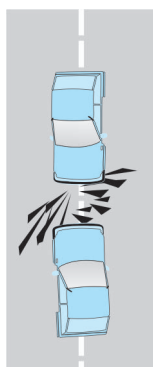
- **Excessive steering wheel movement**



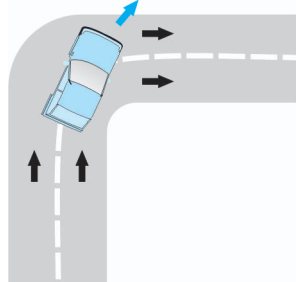
- **Tendency to drive in the middle of the road**



- **Bad judgement**



- **Inaccurate turning (cornering)**



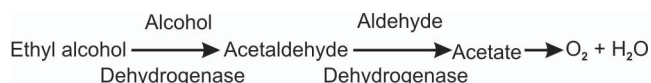
- **Prolonged reaction time and lack of color discriminations.**
- **Delay recovery from dazzle.**
- **Tendency to have accidents on one own.**
- **Over confidence/Excessive caution**

Fig. 11.1.1: Effect of alcohol on motor driving

- Peak plasma concentration attain within 2 hours.
- Distribution occurs throughout the body. Early equilibrium is achieved at that part (organ) of the body with high blood flow, i.e. lung, liver, kidney and brain.

Test for drunk

- Expiratory air concentration $\times 2000$ = Blood concentration
- Urine concentration $\times 77$ = Blood concentration.
- **100 mg% = legally drunk**
- **Metabolism:** Alcohol is metabolized in the liver (>90%) by oxidation. First by alcohol dehydrogenase to acetaldehyde, then by aldehyde dehydrogenase to acetate. About 25% of the acetaldehyde is metabolised extrahepatically (Fig. 11.1.2).



Metabolism of alcohol follows zero order kinetics : a constant amount is metabolized per unit time, i. e. about 10 ml absolute alcohol is metabolized per hour. It is excreted through kidneys and lungs.

- Small amounts of ethanol are excreted in urine and expired air. Hepatic metabolism shows saturation kinetics, mainly because of limited availability of NAD^+ . Maximal rate ethanol metabolism is about 10 ml/hour.

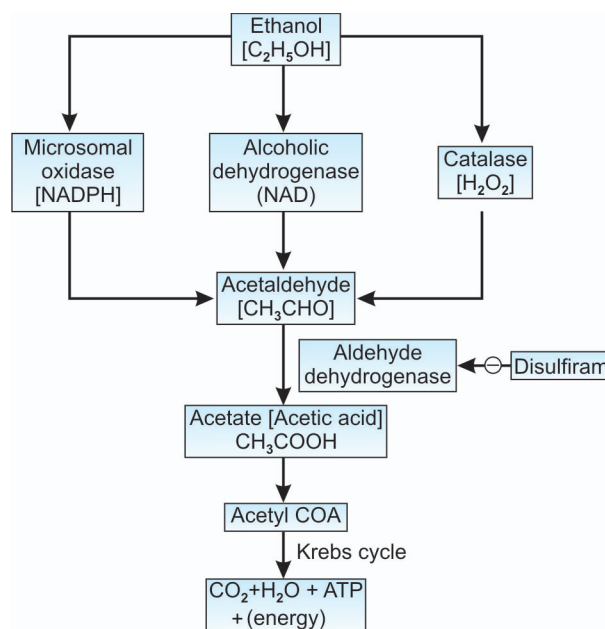


Fig. 11.1.2: Metabolism of ethanol

Thus, plasma concentration falls linearly rather than exponentially.

- Acetaldehyde may produce toxic effects. Inhibition of aldehyde dehydrogenase by disulfiram accentuates nausea discomfort, etc. caused by acetaldehyde, and can be used in aversion therapy.
- Methanol is similarly metabolized to formic acid, which is toxic, especially to retina.
- Asian races show a high rate of genetic polymorphism of alcohol and aldehyde dehydrogenase, associated with alcoholism and alcohol intolerance, respectively.

Mechanism of Action

- Alcohol is amphiphilic, i.e. both hydrophilic and lipophilic, and therefore can dissolve in neural plasma membrane. The mechanism is equivalent to many volatile anesthetic agent, i.e. produces membrane fluidizing effect. Therefore,
- It hampers the movements of Na^+ and Ca^{++} , while movement of Cl^- , specifically stimulation by GABA is increased.

Actions

1. **Local:** On topical application, ethanol evaporates quickly and has a cooling effect. It is an astringent, i.e. precipitates surface proteins and hardens the skin. 40-50% alcohol is rubefacient and counter irritant. Alcohol is also an antiseptic. At 70% it has maximum antiseptic properties (kills > 90% surface bacteria) which decrease above that. It is not effective against spores. Isopropyl alcohol is 60-70% more effective)

Injection around nerve causes neuritis followed by nerve degeneration.

2. **CNS:** Alcohol is a **CNS depressant**. Small doses cause **euphoria**, relief of anxiety and loss of social inhibitions. Moderate doses impair muscular coordination and visual acuity making driving dangerous. (Fig. 11.1.1) With higher doses mental clouding, impaired judgment, drowsiness and loss of self control result. High doses cause stupor and coma. Death is due to respiratory depression. Alcohol may precipitate convulsions in epileptics. Tolerance develops on long-term use. Chronic ingestion results into neurological disorders, i.e.
 - Wernick's encephalopathy (vit. B_1 deficiency, mental confusion, ataxia, polyneuropathy, etc)
 - Korsakoff's Psychosis (learning and memory disability)
 - Sleep disorders.
 - If CNS there occur increase in GABA mediated inhibition, similar to the action of BDZ.
 - Inhibition of Ca^{++} entry through voltage gated calcium channels.
 - Inhibition of NMDA receptor functions.

- Therefore flumazenil reverse the central depressant action of ethanol.

3. **CVS:** The actions are dose dependent. Small doses cause **Cutaneous vasodilatation** resulting in flushing and feeling of warmth. Large (**moderate**) doses cause rise in HDL (High density Lipoprotein) level, depression of myocardium (fall in contractility). Intake in higher (chronic) dose causes development of CCF [congestive cardiac failure] or other Cardiomyopathy, Hypertension and Arrhythmia (death).

4. **GIT and liver:** Alcohol is an irritant (produces Gastritis); increase gastric acid secretion and produces vasodilatation and warmth.

- It causes deficiency of water soluble vitamins and may induce pancreatitis. It is an appetizer in small amount.
- Chronic consumption of moderate amount of alcohol results in peptic ulcer, hepatitis.
- Accumulation of fat in the liver, liver enlargement, followed by fatty degeneration and cirrhosis. Alcohol also induces microsomal enzymes. It may cause alcoholic cirrhosis.

5. **Endocrine:** Though alcohol is called an aphrodisiac (Increases aggressive sex behavior) this effect could be due to loss of inhibition, i.e. (inhibition of control) but ultimately it causes:

- a. Testicular atrophy
- b. Gynecomastia and
- c. Impotence/sterility on long-term consumption.

6. **Musculoskeletal:** It impairs psychomotor performance and blunt the Reflex motor activity (muscle relaxation). Even previously used as an Uterine relaxant (in premature labor).

7. **In pregnant females:** It crosses placenta easily. It produces teratogenic effect called as Fetal Alcohol Syndrome, which is characterized by microcephaly, deficient growth (IUGR) short palpebral fissure, wide eyes, small cheek bone, mental retardation ← hyperactivity + presence of anatomical abnormality.

Other effects

Low doses taken over a long time increases HDL and lowers LDL cholesterol. Alcohol is a diuretic ($\downarrow$ ADH secretion). It interferes with folate metabolism and may cause megaloblastic anemia. Though it causes a feeling of warmth, heat loss is increased due to vasodilatation and should not be used for 'warming up' in cold surroundings. Food value is 7 calories/gram. It may stimulate respiration.

Uses

1. Sponging on body surface for decreasing body temperature.

2. It acts as an Antiseptic/disinfectant, if 70% alcohol is applied topically.
3. **Bed sores (decubitus ulcer):** when rubbed onto the skin, alcohol hardens the skin and prevents bed sores.
4. **As anhydrotic lotion:** to reduce sweating.
5. **Appetite stimulant:** About 50 ml of 6-10% alcohol given before meals is an appetite stimulant.
6. **Neuralgias:** In severe neuralgias like trigeminal neuralgia, injection of alcohol around the nerve causes permanent loss of transmission and relieves pain.
7. As a solvent or vehicle for injecting medicinal mixture.
8. **Brampton's mixture:** It is the mixture of alcohol, opioid and or phenothiazine used sometimes to relieve pain of terminal illness.
9. In **methanol or ethyl glycol poisoning.**
10. Rarely used to **treat premature labor:** Its 10% solution suppresses the uterine contraction by reducing the release of oxytocin.

Drug interactions

1. Alcohol potentiates other CNS depressants including hypnotics, opioids and anti-psychotics.
2. Sulfonyleureas, (chlorpropamide) metronidazole, griseofulvin and certain cephalosporins have disulfiram like effects on alcohol consumption.
3. Alcohol is an enzyme inducer.
4. Alcohol with NSAIDs ® more GIT bleeding.
5. Alcohol + Insulin or sulfonyleurea ® - hypoglycemia

Acute alcoholic intoxication: It causes severe gastritis, hypotension, hypoglycemia, hypothermia, disturbed sensorial, hypostatic pneumonia, increased intracranial pressure, respiratory depression, coma and death.

Treatment

- Measures include gastric lavage, airway maintenance, positive pressure ventilation and maintenance of fluid and electrolyte balance.
- Maintenance of BP, Temperature and Hemodialysis is needed in severe intoxication.
- Administration of hypertonic mannitol IV.
- Phenothiazine/butryphenon is administered to control psychotic behavior.
- Analeptics are not recommended (produces convulsions).

Chronic alcoholism causes

- Both tolerance and dependence are due to increased metabolism and neuronal receptor adaptation.
- **Withdrawal symptoms:**
 - **Stage I:** Nausea, vomiting, sweating, tremors and hyperactivity
 - **Stage II:** Auditory and visual hallucination.

- **Stage III:** Delirium, tremors, confusion, disorientation, autonomic hyperactivity and other systemic toxicity and later on.
- Wernicke's encephalopathy, Korsakoff's psychosis, tremors, cirrhosis of liver, hypertension and cardiomyopathy can occur.
- In addition, nutritional deficiencies such as polyneuritis, anemia and pellagra can occur. In pregnant women, alcohol is teratogenic. Even moderate drinking during pregnancy can produce **fetal alcohol syndrome** with manifestations like low IQ, microcephaly, growth retardation and facial anomalies. It can also cause stillbirths and abortions.

Treatment

- Multivitamin tablet/capsule (specially vitamin B₆).
- Treatment of acidosis
- **Benzodiazepine** (DOC) for supporting withdrawal symptoms.
- Using **Disulfiram** (Tetraethyl thiuram disulfide): discussed below.
- Using **Naltrexone** (opioid antagonists): It reduces alcohol consumption and craving probably by inhibiting dopaminergic pathway in the brain which is critical for reward phenomenon.
- **Daidzine:** It is a Chinese herbal medicine and is a specific inhibitor of ALDH -1
- **Nalmefene:** It has better oral bioavailability, less hepatotoxic and longer duration of action as compared to naltrexone.
- **Using Acamproste:** It GABA analog and NMDA antagonist. It reduces neuronal hyper-excitability and inhibits alcohol craving.
- Using **Fluoxetine**
- Psychiatric counseling: for complete abstinence from alcohol.
- **Supportive management.**
Including symptomatic treatment, i.e T/t with β -blockers, clonidine, etc.

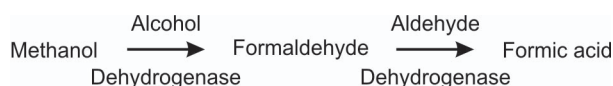
Disulfiram

- Disulfiram inhibits the enzyme aldehyde dehydrogenase. (Fig. 11.1.2) If alcohol is consumed after taking disulfiram, acetaldehyde accumulates and within few minutes it can produce flushing, throbbing headache, nausea, vomiting, sweating, hypo $\rightarrow$ $\leftarrow$ tension and confusion called the **ant abuse reaction**, due to accumulation of acetaldehyde. The effect lasts for 7-14 days after stopping disulfiram. The reaction can sometimes be very severe and therefore treatment should be given in a hospital.

- Other drugs that cause ant-abuse reaction are metronidazole, chlorpropamide, tolbutamide, griseofulvin, cephalosporins and phenyl-butazone.
- Contraindications: Patients with liver disease, patients physically dependant on alcohol.

METHYL ALCOHOL (Methanol, Wood Alcohol).

Methanol is used to denature ethyl alcohol, Ingestion results in methanol poisoning.



Toxic effects are due to formic acid. Manifestations are vomiting, headache, vertigo, severe abdominal pain, hypotension, delirium, acidosis and coma. Formic acid has affinity for optic nerve and causes retinal damage resulting in blindness. Death is due to respiratory failure.

Treatment

Correction of acidosis: As acidosis hastens retinal damage, immediate correction of acidosis with IV sodium

bicarbonate infusion helps in preventing blindness, i.e. NaHCO_3 infusion (3 gm/hr) until pH rises up to 7.5

1. Patient should be kept in a dark room to protect the eyes from light.
2. Induction of vomiting.
3. Gastric lavage should be given.
4. Multivitamins tablets specially Vitamin B should started.
5. Ethyl alcohol (**Ethanol**): Ethyl alcohol is given as infusion or 25 ml 50%, 3 hourly till the acidosis is controlled. It competes with methanol for alcohol dehydrogenase, slows the metabolism of methanol and thus prevents the formation of toxic metabolites.
6. **Fomepizole**: 4 methyl pyrazole, is the specific antidote. It also inhibits alcohol dehydrogenase so as to prevent formation of toxic metabolite.
7. **Folinic acid**: It may protect ocular toxicity by increasing formate metabolism.
8. BP and ventilation should be maintained (Positive pressure ventilation).
9. Diuretics/Dialysis
10. Supportive management.

Chemical Transmission in the Nervous System

The processes of synaptic transmission in the CNS are more or less similar to those operating in the PNS.

- The terms 'neurotransmitter', 'neuromodulator' and 'neurotrophic factor' are defined as:
 - **Neurotransmitters:** are the chemicals released by presynaptic terminals and produce rapid excitatory or inhibitory responses in postsynaptic neurons (Fig. 11.2.1).
 - **Neuromodulators:** are the chemicals released by neurons, and produces slower pre- or postsynaptic

responses, mediated mainly by G-protein-coupled receptors.

- **Neurotrophic factors:** they are released mainly by non-neuronal cells and act on tyrosine-kinase-linked receptors which regulate gene expression, and control neuronal growth and phenotypic characteristics.
- Neurotransmitters may be broadly divided into:
 - **Fast neurotransmitters:** operating through ligand-gated ion channels (e.g. glutamate, GABA)

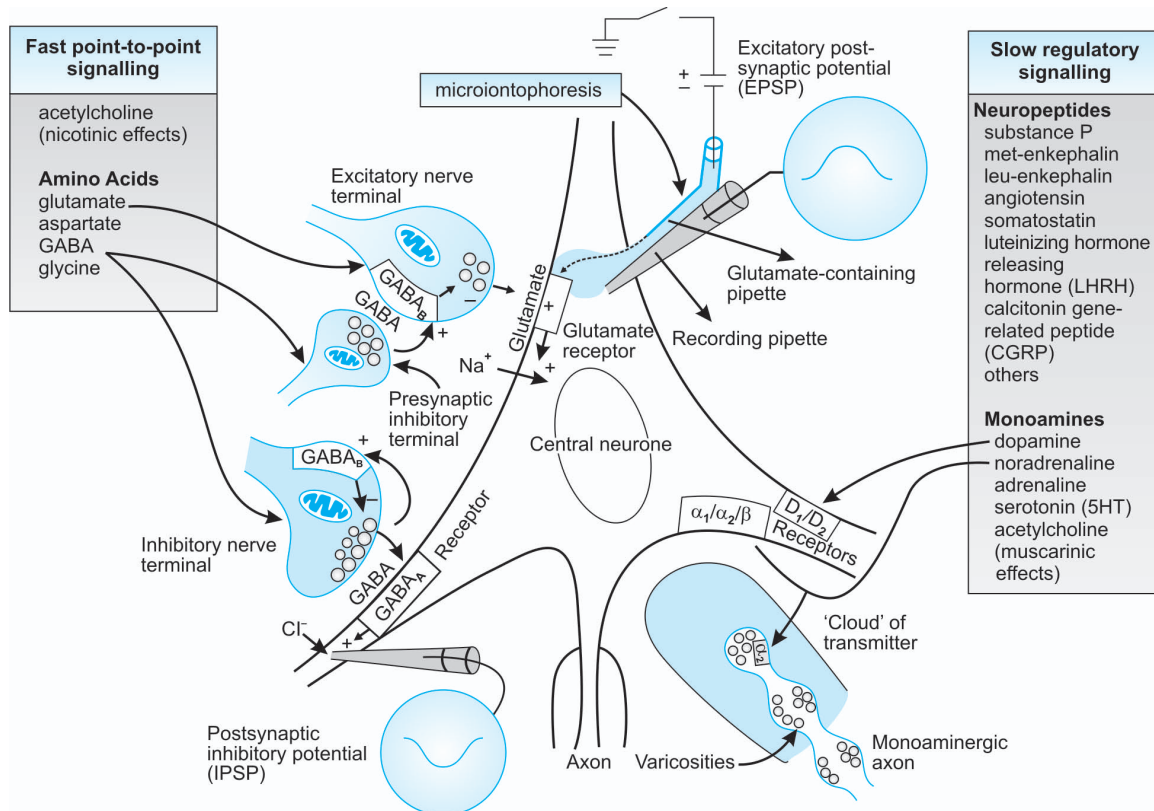


Fig. 11.2.1: Central transmitter substances

- **Slow neurotransmitters and neuromodulators:** operating mainly through G-protein-coupled receptors (e.g. dopamine, neuropeptides).
- The same agents (e.g. **glutamate, 5-HT, acetylcholine**) may act through both ligand-gated channels and G-protein-coupled receptors.
- Other neuromodulators, including **nitric oxide** and **arachidonic acid metabolites**, may be produced by non-neuronal cells as well as neurons.
- Many other mediators (e.g. cytokines, growth factors, steroids) are postulated to control long-term changes in the brain (e.g. synaptic plasticity, remodeling, etc.), mainly by affecting gene transcription.

Excitatory amino acids: EAAs, namely glutamate and aspartate, are the main fast excitatory transmitters in the CNS.

- Glutamate is formed mainly from the Krebs cycle intermediate, α -oxoglutarate, by the action of GABA-(amino-transferase)
 - There are four main EAA receptor subtypes:
 - NMDA
 - AMPA
 - Kainite
 - Metabotropic
- NMDA, AMPA and kainate receptors are directly coupled to cation (+) channels, metabotropic receptors act through intracellular second messengers.
- The channels controlled by NMDA receptors are highly permeable to Ca^{2+} and are blocked by Mg^{2+} .
- AMPA and kainite receptors are involved in fast excitatory transmission, NMDA receptors mediate slower excitatory responses and, though their effect in controlling Ca^{2+} entry, play a more complex role in controlling synaptic plasticity (e.g. long-term potentiation).
- Metabotropic receptors are G-protein-coupled receptors, linked up IP_3 formation and intracellular Ca^{2+} release. They play a part in glutamate-mediated synaptic plasticity and excitotoxicity. Specific agonists and antagonists are known.
- EAA receptor antagonists have yet to be developed for clinical use.

Inhibitory Amino Acids: GABA and Glycine

GABA is the main inhibitory transmitter in the brain

- It is present uniformly throughout the brain.
- GABA is formed from glutamate, by the action of GAS (glutamic acid decarboxylase). Its action is terminated mainly by reuptake, but also by deamination, catalysed by GABA-transaminase.
- There are two type of GABA recetpor, GABA_A and GABA_B .
- **GABA_A recetpors**, which occur mainly postsynaptically, are directly coupled to chloride channels, opening of which reduces membrane excitability. Muscimol is a specific GABA_A agonist, and the convulsant, Bicuculline is an antagonist.
- **GABA_B receptors** are G-protein-coupled receptors, linked to inhibition of cAMP formation. They cause pre- and postsynaptic inhibition by inhibiting Ca^{2+} channel opening and increasing K^+ conductance. Baclofen is a GABA_B receptor agonist, used to treat spasticity. GABA_B antagonists are not yet in clinical use.
- **Glycine** is an inhibitory transmitter mainly in the spinal cord, acting on its own receptor, which functionally resembles the GABA_A receptor.
- The convulsant drug, **strychnine**, is a competitive glycine antagonist. **Tetanus toxin** acts mainly by interfering with glycine release.

Noradrenaline in the CNS

- Mechanisms for synthesis, storage, release and reuptake of nor adrenaline in the CNS are absolutely same as in the periphery. And receptors are also same.
- Nor-adrenergic pathways, running mainly in the medial forebrain bundle, descending spinal tracts, and terminate diffusely in the cortex, hippocampus, hypothalamus, cerebellum and spinal cord.
- The actions of noradrenaline are mainly inhibitory (β -receptors), but some are excitatory. The 'arousal' system, controlling wakefulness and alertness; blood pressure regulation: control of mood (functional deficiency contributing to depression), and function of 'reward system'.
- **Psychotropic drugs that act party or mainly on noradrenergic transmission in the CNS include:** antidepressants, cocaine, amphetamine. Some antihypertensive drugs (e.g. clonidine, methyl dopa) act mainly on noradrenergic transmission in the CNS.

Dopamine in the CNS

- **Dopamine** is a neurotransmitter as well as being the precursor for nor adrenaline. It is degraded in a similar fashion for nor adrenaline, giving rise mainly to DOPAC and HVA, which are excreted in the urine.
- There are three main dopaminergic pathways:
 - **Nigrostriatal pathway**, important in motor control
 - **Mesolimbic/mesocortical pathways**, running from groups of cells in the midbrain to parts of the limbic system, especially the nucleus accumbens, and to the cortex; they are involved in emotion and drug-induced reward systems.

- There are two main families of dopamine receptor: D_1 and D_2 , linked, respectively to stimulation and inhibition of adenylate cyclase. The D_1 family comprises D_1 and D_5 subtypes. The known functions of dopamine appear to be mediated mainly by receptors of the D_2 family.
- Receptors of the D_2 family may be implicated in **schizophrenia**. The D_4 -receptor shows marked polymorphism in humans.
- **Parkinson's disease** is associated with a deficiency of nigro-striatal dopaminergic neurons.

5-Hydroxy-Tryptamine in the CNS

- The processes of synthesis, storage, release, reuptake and degradation of 5-HT in the brain are very similar to events in the periphery.
- Availability of tryptophan is the main factor regulating synthesis.
- Urinary excretion of 5-HIAA provides a measure of 5-HT turnover.
- 5-HT neurons are concentrated in the midline raphe nuclei in the pons and medulla, projecting diffusely to the cortex, limbic system, hypothalamus and spinal cord, similar to the noradrenergic projections.
- The main receptor subtypes in the CNS are 5-HT_{1A} , 5-HT_{1B} , 5-HT_{1D} , 5-HT_2 , 5-HT_3 . Associations of behavioral and physiological functions with these receptors have been partly worked out. Other receptor types (5-HT_{4-7}) also present in the CNS, but little is known about their functions.

Acetylcholine in the CNS

- Synthesis, storage and release of acetylcholine in the CNS are same as in the periphery.
- ACh is widely distributed in the CNS.
 - Basal forebrain nuclei, which send a diffuse projection to most forebrain structures
 - Short interneurons in the striatum and nucleus accumbens
 - Recurrent inhibitory pathways from spinal motor neurons.
- Certain neurodegenerative diseases, especially dementia and Parkinson's are associated with abnormalities in cholinergic pathways.
- Both nicotinic and muscarinic ACh receptors are present in the CNS. The former mediate the central effects of nicotine. There are few example of transmission mediated by postsynaptic nicotinic receptors.
- Muscarinic receptors appear to mediate the main behavioral effects associated with ACh, namely effects on arousal, and on learning and short-term memory.

Other Transmitters and Modulators

Histamine: Histamine fulfill the criteria for a neurotransmitter. Histaminergic neurons originate mainly in the hypothalamus, and have a widespread distribution.

Purines:

- Both adenosine and ATP function as transmitters and/or neuromodulators but the neuronal pathways have not yet been defined.
- **Adenosine** exerts mainly inhibitory effects, through A_1 - and A_2 -receptors resulting in sedative, anticonvulsant and neuroprotective effects,
- **Methylxanthines** (e.g. caffeine) are antagonists at A_2 -receptors, and increase wakefulness.

Melatonin

- Melatonin is synthesized from 5-HT, mainly in the pineal gland from which it is released as a circulating hormone.
- Secretion is controlled by light intensity, being low by day and high by night. Fibers from the retina run to the suprachiasmatic nucleus ('biological clock') which controls the pineal gland via its sympathetic innervations.
- Melatonin acts on several types of receptor in the brain and periphery. Given orally, it causes sedation, and also 'resets' the biological clock being used for this purpose to counter jet-lag.

Nitric oxide: Neuronal NOS is present in many CNS neurons and NO production is increased by mechanisms (e.g. transmitter action) which raise intracellular Ca^{++} .

- NO affects neuronal function by increasing cGMP formation, producing both inhibitory and excitatory effects on neurotoxicity.
- Carbon monoxide shares many properties with NO.
- Arachidonic acid produced in neurons by receptor-mediated hydrolysis of phospholipid. It is converted to various eicosanoids and to other metabolites.
- Excitotoxicity is associated mainly with activation of NMDA receptors, but other types of EAA receptors also contribute.
- Excitotoxicity can occur under pathological conditions (e.g. cerebral ischemia) in which excessive glutamate release occurs. It can also occur when chemicals such as kainic acid are administered.
- **Oxidative stress** refers to conditions (e.g. hypoxia) in which the protective mechanisms are compromised, and neurons become more susceptible to excitotoxic damage.
- Excitotoxicity due to environmental chemicals may contribute to some neurodegenerative disorders.

Drugs used in Parkinson's Disease and Alzheimer's Disease

Parkinson Disease: [one of the classical example of **Neuro-degenerative disease**]

Definition: It is an chronic, progressive, extrapyramidal motor disorder characterized by:

- **Hypokinesia or bradykinesia:** (decreased movement)
- **Rigidity,** (increased resistance in passive limb movement) and
- **Tremors:** At rest (specially pin rolling tremors) decreased during voluntary activity.

The secondary manifestation includes

- Defective posture.
- Defective gait (shuffling gait)
- Mask like face.
- Sialorrhea (increased salivation)
- Dementia (loss of memory)
- *Progresses to:*
 - Rigid patients
 - Unable to move
 - Unable to breath
 - Chest infection/embolism
 - Death (sometime)
- It was described by **James Parkinson in 1817** and is therefore named after him.
- The incidence is about 1% of population above 60 years of age.
- It is a Degenerative disease of the basal ganglia
- Often idiopathic, but may follow stroke, viral infection or can be drug-induced (neuroleptic drugs).
- In idiopathic Parkinson's disease, there is degeneration of nigrostriatal neurons in the basal ganglia resulting in dopamine deficiency (Fig. 11.3.1).
- The balance between inhibitory dopaminergic neurons and excitatory cholinergic neurons is disturbed.
- Can be induced by MPTP, a neurotoxin affecting dopamine neurons in the corpus striatum.

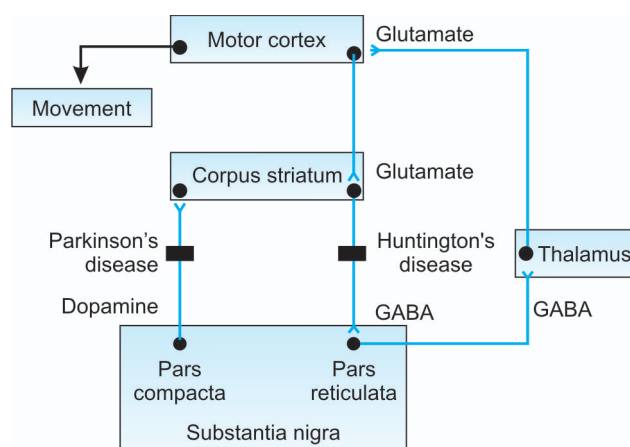


Fig. 11.3.1: Defects in organization in extrapyramidal motor system in Parkinson's and Huntington's disease.

Antiparkinsonian Drugs (Fig. 11.3.2)

It can only help to alleviate the symptoms and improve the quality of life. The two strategies in the treatment are (i) to enhance dopamine activity by its substitution, by increase in release of DA and by inhibiting its destruction. (ii) to depress cholinergic overactivity.

CLASSIFICATION (Fig. 11.3.3)

1. Drugs that increase dopamine levels in the brain

- DA precursor: Levodopa.
- Peripheral DOPA decarboxylase inhibitors: carbidopa and benserzide
- Drug that release dopamine: Amantadine
- Dopaminergic agonists: Bromocriptine, Lysuride, prergolie, ergoline
- Inhibit dopamine metabolism [MAO inhibitors:] Selegiline and Rasagiline.
- COMT Inhibitors (They ↑ bioavailability of L-Dopa: tolcapone, entacapone)

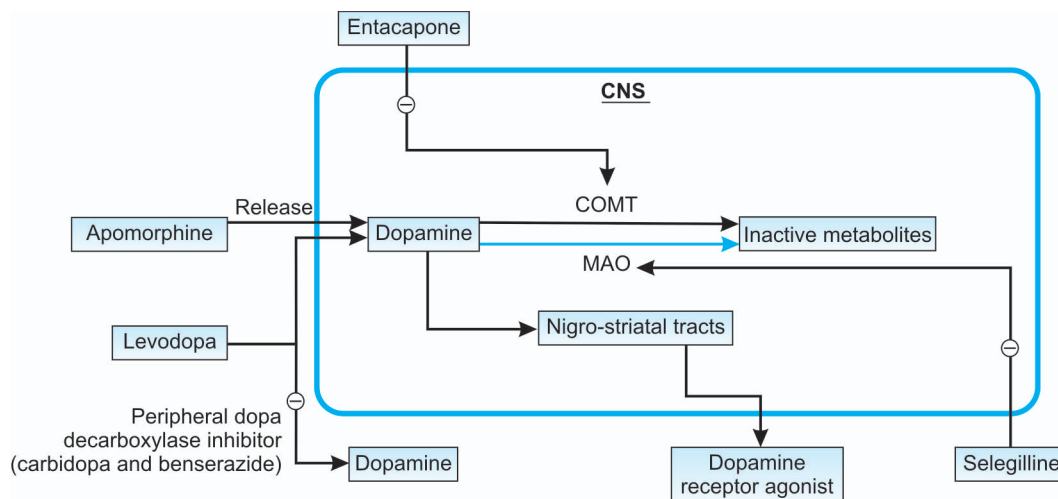


Fig. 11.3.2: Drug treatment for Parkinson's disease

2. Drugs influencing cholinergic system

- I. **Central anticholinergic drugs.** Benztropine, Benhexol, Biperidine, Trihexyphenidyl
- II. **Antihistamines.** Diphenhydramine, Orphenadrine, Promethazine.
3. **Apomorphine** → Dopamine agonist (V-potent)

LEVODOPA (L-dopa)

- Parkinsonism is due to dopamine deficiency yet, dopamine is of no therapeutic value because it does not cross the Blood-Brain-Barrier.
- Levodopa is a prodrug which is converted to dopamine in the body. It crosses the Blood-Brain-Barrier and is taken up by the surviving nigrostriatal neurons.

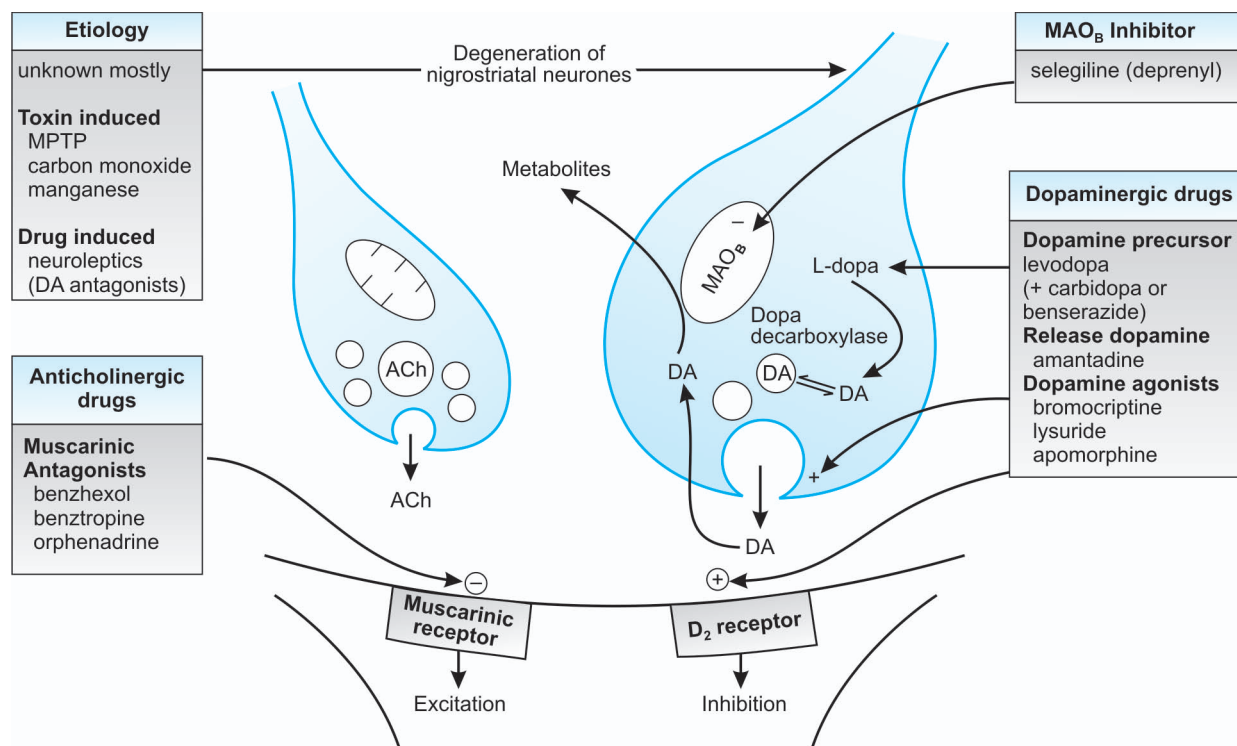


Fig. 11.3.3: Drugs used in Parkinsonism

Pharmacokinetics

- Levodopa is well absorbed from the small intestine; however, 95% is rapidly decarboxylated in the periphery.
- Peripheral dopamine is metabolized in the liver to dihydroxy-phenyl-acetic acid (DOPAC) and homovanillic acid (HVA), which are then excreted in the urine.

Mechanism of action: Dopamine deficiency in the striatum needs to be corrected in the treatment of parkinsonism.

1. Dopamine does not cross the Blood-Brain-Barrier; thus, levodopa, the precursor of dopamine, is given instead.
2. Levodopa is formed from L-tyrosine and is an intermediate in the synthesis of catecholamines.
3. Levodopa itself has minimal pharmacological activity, in contrast to its decarboxylated product, dopamine.
4. Levodopa is rapidly decarboxylated in the gastrointestinal tract. Prior to the advent of decarboxylase inhibitors (carbidopa), large oral doses of levodopa were required; thus, toxicity from dopamine was a limiting factor.
5. Sinemet treatment: In this regimen: 25 mg of carbidopa and 100 mg of Levodopa is given TDS or QID, at least 30 to 60 min. prior to meal.

Pharmacological effects

1. The effects on bradykinesia and rigidity are more rapid and complete than the effects on tremor. Other motor defects in Parkinson's disease improves. The psychological well-being of the patient is also improved.
2. Tolerance to both beneficial and adverse effects occurs with time. Levodopa is most effective in the first 2-5 years of treatment. After 5 years of therapy, patients have dose-related dyskinesias, inadequate response, or toxicity.

Other actions

- **CTZ**—Dopamine stimulates CTZ to induce vomiting.
- **Endocrine**—Dopamine suppresses prolactin secretion.

Adverse effects: Because the decarboxylation of levodopa increases peripheral concentrations of dopamine, prominent α - and β -adrenergic effects are seen, but these effects are significantly less severe than those seen with epinephrine, nor epinephrine, or isoproterenol.

Principal Adverse Effects Include

- Anorexia, nausea, and vomiting (due to CTZ stimulation) upon initial administration, which often limits the initial dosage. Tolerance may be developed to these effects.
- Cardiovascular effects, including tachycardia, arrhythmias, and orthostatic hypotension

- Mental disturbances, including vivid dreams, delusions, hallucinations and behavioral abnormality.
- Sudden discontinuation can result in fever, rigidity, and confusion. The drug should be withdrawn gradually over 4 days.
- **ON-OFF phenomenon:** In few patients of parkinsonism with stabilized long-term treatment with levodopa, fluctuation in clinical state unrelated to the timing of doses develops. The 'off' period in phenomena presents, with marked akinesia alternate over the course of a few hours with 'on' periods of improved mobility.
- **Treatment:** Apomorphine could be given with a drug holiday for 3 to 7 days.

Drug interactions

- Pyridoxine reduces the beneficial effects of levodopa by enhancing its extracerebral metabolism. the decarboxylation of levodopa to dopamine is mediated by an enzyme that is pyridoxine-dependent.
- Phenothiazines, reserpine, and butyrophenones antagonize the effects of levodopa because they lead to a junctional blockade of dopamine action.
- Therapy with monoamine oxidase (MAO) inhibitors must be stopped 14 days prior to the initiation of levodopa therapy.
- Dietary amino acids can decrease effectiveness of levodopa by competing for absorption from the intestine.
- Fate of levodopa and carbidopa is shown in Fig. 11.3.4a and 11.3.4b.

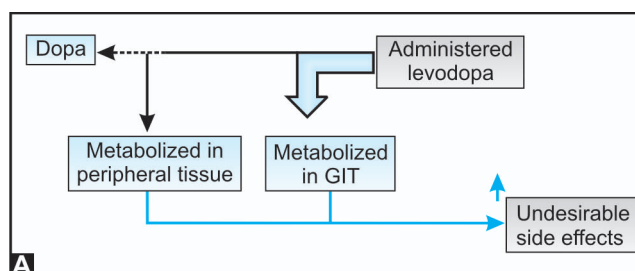


Fig. 11.3.4a: Fate of Levodopa

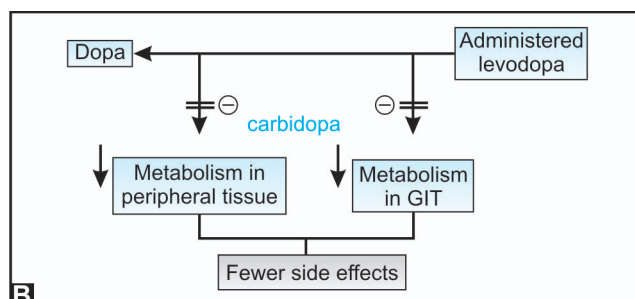


Fig. 11.3.4b: Fate of levodopa and carbidopa

Carbidopa and Benserazide

- They are peripheral dopa-decarboxylase inhibitors. When carbidopa or benserazide are given with levodopa, they prevent the formation of dopamine in the periphery.
- They do not cross the BBB and hence allow levodopa to reach the CNS. The combination is synergistic and therefore levodopa is always given with carbidopa/benserazide.

Pharmacokinetics

- Levodopa blood levels are increased, and drug half-life is lengthened, if administered with carbidopa or Benserazide
- The dose of levodopa can be significantly reduced, also reducing toxic side effects.
 1. A shorter latency period precedes the occurrence of beneficial effects.
 2. If the patient has been taking levodopa alone, it should be withheld for 8 hours before starting combined carbidopa-levodopa therapy, and the dosage of levodopa should be reduced by 75%.
 3. Side effects like vomiting and tachycardia are greatly reduced.

Preparations: **Sinemet** is the trade name of a preparation that combines carbidopa and levodopa in fixed proportions (1:10 and 1:4). It is considered the most effective treatment for Parkinson's disease.

Adverse effects: Adverse effect of the combination are similar to those seen with high doses of levodopa.

Amantadine**Mechanism of action and therapeutic indications**

- Amantadine is an antiviral agent used in the prophylaxis of influenza A₂. It was found to improve parkinsonian symptoms by stimulating the release of dopamine from dopaminergic nerve terminals in the nigrostriatum and delaying its reuptake.
- Amantadine may be more efficacious in parkinsonism than the anticholinergic atropine derivatives but is less effective than levodopa. It has been used alone to treat early Parkinson's disease and as an adjunct in later stages.

Excretion: Amantadine is well absorbed orally and is excreted unchanged in the urine.

Adverse effects: These are infrequent; however, long-term use can produce iteics reticularis in the lower extremities. Tolerance is observed in 6-8 weeks.

Bromocriptine and pergolide: Bromocriptine is an ergot derivative having dopamine agonistic activity at D₂ receptors.

Mechanism of action and therapeutic indications

- Bromocriptine and pergolide provide additional therapeutic benefit when added to levodopa therapy, but have less antiparkinsonian effect than levodopa.
- As ergot derivatives, bromocriptine and pergolide mimic the action of dopamine.
- They are used in a doses of 1.25-30 mg BD.

Adverse effects

- Such as hallucinations, postural hypotension, and livedo reticularis are more common with bromocriptine than with levodopa; however, it induces less dyskinesia than levodopa.
- Lisuride and pergolide are similar to bromocriptine.

Selegiline (Deprenyl and Rasagiline): Selective MAO-B inhibitor:

Mechanism of action: Selegiline is a selective MAO type B inhibitor, also known as deprenyl.

Therapeutic use:

- Treatment with selegiline postpones the need for levodopa for 6-9 months.
- Selegiline may delay the progression of parkinsonism.
- It is also used as an adjunct to levodopa.
- Dosage: 5 mg BD.

Adverse effects:

- Unlike MAO-A inhibitors (used for depression), selegiline does not cause hypertension after ingesting tyramine-rich foods.
- Fluoxetine and meperidine have been associated with toxic reactions when taken with selegiline.

Anticholinergic Agents: Benztropine, Benzhexol**Mechanism of action**

- Since the deficiency of dopamine in the striatum augments the excitatory cholinergic system in the striatum, (CNS). The blockade of this system by anticholinergic agents, such as trihexyphenidyl, helps to alleviate the motor dysfunction.
- Improvement in the parkinsonian tremor is more pronounced than improvement in bradykinesia and rigidity.

Therapeutic uses: Although not as effective as levodopa or bromocriptine, anticholinergic agents may have an additive therapeutic effect at any stage of the disease when taken concurrently.

- In drug induced Parkinsonism : Drug of choice

Adverse effects: such as mental confusion and hallucinations due to central muscarinic toxicity, can occur as peripheral atropine-like toxicity (e.g. cycloplegia, urinary retention, constipation).

Antihistamines: (e.g., diphenhydramine) are less effective therapeutically but are better tolerated than anticholinergic agents.

Antidepressants: Depression commonly accompanies Parkinson's disease. A tricyclic antidepressant or trazodone is usually the drug of choice.

Drug induced parkinsonism:

- Drugs like reserpine, metoclopramide and phenothiazines can induce parkinsonism.
- Reserpine depletes catecholamine stores, metoclopramide and phenothiazines are dopamine antagonists.

Treatment: Withdrawal of the drug usually reverses the symptoms. When drugs are needed, one of the anticholinergics are effective.

DEMENTIA AND ALZHEIMER'S DISEASE

- Alzheimer's disease (AD) is a common age-related dementia distinct from vascular dementia associated with brain infarction.

- The main pathological features of AD comprise amyloid plaques neurofibrillary tangles, and a loss of neurons (particularly cholinergic neurons of the basal forebrain).
- Amyloid plaques consist of the AB fragment of amyloid precursor protein (APP), a normal neuronal membrane protein. The causes of excessive AB formation are not known, but may include: mutations affecting APP; excessive phosphorylation of APP; abnormal APP proteases. There is some evidence that AB is neurotoxic,
- Neurofibrillary tangles comprise aggregates of a highly phosphorylated form of a normal neuronal protein. The relationship of these structures to neurodegeneration is not known.
- Loss of cholinergic neurons is believed to account for much of the learning and memory deficit in AD.
- Currently available therapies for AD are only marginally effective at best; most have shown little or no benefit in controlled trials: Anticholinesterases [tracrine, donepezil] give proven, though limited, benefit].
- Other drugs, including vasodilators (dihydroergotoxine), muscarinic agonists (arecholine, pilocarpine), give no demonstrable benefit, and are not officially approved.

General Anesthetics

Definition: The state of general anesthesia (GA) usually includes:

- Analgesia
- Amnesia
- Reversible loss of consciousness
- Inhibition of sensory and autonomic reflexes and
- In many cases skeletal muscle relaxation
[All these cardinal features must be reversible]

No single drug (anesthetic agent) is capable of achieving all of these desirable effects without some disadvantages when used alone, therefore modern practice of anesthesia most commonly involves the use of combination of drugs to produce balanced anesthesia.

Balanced anesthesia: It is not possible to achieve ideal anesthesia with a single drug, therefore multiple drugs are used to produce this ideal state, i.e. ideal anesthesia for example - preanesthetic medication, IV anesthetics for induction, inhalational agents for maintenance, oxygen, skeletal muscle relaxants and analgesics. This is called balanced anesthesia.

For the purpose of safe surgery we can categorize the surgical period as preoperative, intraoperative and postoperative periods.

1. Preoperative period

- a. Anesthetic assessment for selection of anesthetic agent.
- b. Preanesthetic medications

2. Intraoperative period

- a. Anesthesia (anesthetics)
- b. Therapeutic monitoring for various vital functions

3. Postoperative period

- a. Recovery
- b. Relief of nausea, vomiting and pain
- c. Care of various vital functions

History of Anesthesia

- Before 1846, surgery was uncommon. During ancient time, alcohol, opium, packing a limb with ice and concussion, i.e. making the patient unconscious by a blow on the head, strangulation, making a limb ischemic with a tourniquet, were used to relieve the surgical pain.
- **Priestley** (1776) synthesizes N_2O (Laughing gas)
- **Davy** (1790), first comments about the anesthetic property of N_2O [Laughing gas].
- **Dr Horace Wells** (1844) a dentist, tried to demonstrate the effect of nitrous oxide as an anesthetic in 1844 but was unsuccessful as he removed the gas bag too early.
- **Dr William Morton** who was present at the demonstration, worked on it and in 1846 demonstrated ether anesthesia successfully on *Gilbert Abbott* (patient). The surgeon was **Dr. Warren**.
- **Jams Simpson** worked out chloroform (1847)
- Since then several anesthetics have been synthesized over the decades.
- Cyclopropane was introduced in 1929, while halothane in 1956.

Stages of General Anesthesia (ether)

• There occurs irregular depression of CNS

It is divided into three stages: **1) Induction, 2) Maintenance and 3) Recovery.**

- In brain higher functions are lost first followed by lower functions while.
- In Spinal cord lower segment affected first followed by higher segment.
- Vital functions (medulla) affected lastly.

I. Stage of analgesia

- It is from the beginning of inhalation to loss of consciousness.

- Initially there occurs analgesia without amnesia, later on analgesia with amnesia.
- Patient can hear/see/dream like state
- There occurs; increase in the heart rate, and dilatation of pupil.
- Reflexes and respiration are normal.

II. Stage of Excitement/delirium

- This stage is from loss of consciousness to onset of regular respiration, i.e. beginning of surgical anesthesia.
- It may be associated with excitement-shouting, crying, struggling, and violent behavior. Some time involuntary micturition may occurs.
- Patients are delirious and excited (amnesic).
- Respiration: irregular and jerky, pupil: dilated (sympathetic stimulation), increase in the skeletal muscle tone (struggle) and rise in blood pressure and heart rate.

III. Stage of surgical anesthesia

- This stage is begins with recurrence of regular respiration and extends up to complete cessation of spontaneous respiration.
- This has 4 planes. As anesthesia passes to deeper planes, respiratory depression is seen. There is gradual loss of reflexes and relaxation of skeletal muscles.
 - Plane 1:** Normal pupil, rolling eyeball.
 - Plane 2:** Slightly dilatation of pupil/loss of corneal and pharyngeal reflexes.
 - Plane 3:** Dilatation of pupil/loss of light reflex
 - Plane 4:** Full dilatation of pupil/stoppage or complete abdominal breathing (intercostals paralysis).

IV. Stage of medullary paralysis

- It is seen only with overdose. It is the stage of medullary depression → cessation of breathing, circulatory failure and death may occur.
- Pupil widely dilated, muscles flabby, pulse thready (weak) and BP very low.

Pharmacokinetics

Ficks law: Simple diffusion of gases are based on this ficks law

$$dq/dt = (-D)(A)(dc/dx)$$

Where

dq/dt = is the rate of drug flux, i.e. change in drug concentration at given time,

D = Temperature dependent different constants,

A = Area of absorbing surface, and

dc/dx = Concentration gradient.

- According to **ficks law**, if there is higher the concentration gradient, higher be the rate of absorption.
- If larger the surface area, larger be the drug flux.
- D is directly proportional to T (temperature) while inversely proportional to molecular size.
- If higher be the lipid-water partition coefficient, higher be the drug flux.

General Considerations

Minimal Alveolar Concentration (MAC): It is the minimum (lowest) concentration of anesthetic agent in the alveoli required to produce immobility in 50% of patients on giving painful stimuli (surgical incision).

- MAC:** is the index of potency for a particular anesthetic agent.
- Depth of anesthesia depends upon:
 - Potency of general anesthesia and
 - Its partial pressure in brain.

Alveoli = Blood = Brain

- The relationship between the administered dose of an inhalation anesthetic and the quantitative effect produced is described as the minimum alveolar concentration (MAC) of the anesthetic at 1 atmosphere that will produce loss of movement in 50% of subjects exposed to a noxious stimulus. The MAC is used as the measure of potency for all inhalation anesthetics.
- The concentration of an inhalational anesthetic in blood or tissue is the product of its solubility and partial pressure. The solubility of an agent is expressed most commonly in terms of a blood : gas or a tissue : blood partition coefficient.
 - An agent with a blood: gas partition coefficient of 2 reaches twice the concentration in the blood phase as in the gas phase when the partial pressure is the same in both phases (i.e., at equilibrium). Very soluble agents (e.g., ether) have a blood : gas partition coefficient as high as 12; relatively insoluble agents (e.g., nitrous oxide) have coefficient of less than 1. The lower the blood : gas partition coefficient of an anesthetic, the more rapid the induction of anesthesia with that agent, because high blood solubility constantly lowers the alveolar gas pressure.
 - Most inhalation agents are equally soluble in lean tissue and in blood, so that the tissue: blood partition coefficient often approximates 1. On the other hand, most anesthetics have a far greater concentration in fatty tissue than in blood at equilibrium.

The rate at which a given concentration of anesthetic agent in the brain is reached depends on the following factors:

1. Partial pressure of the anesthetic agent in the inspired gas:

Partial pressure is directly proportional to concentration of the drug (anesthetic agent) in the inhaled mixture of gases.

- Higher be the concentration - Higher be the partial pressure - Higher be the transferred rate to the blood.

2. Pulmonary ventilation:

- Hyperventilation increases concentration of anesthetic agent in the alveoli and therefore increases the transferred rate to the blood.
- Hypoventilation decreases concentration of anesthetic agent in the alveoli and therefore decreases the transferred rate to the blood.

3. Alveolar exchange: Gases diffuses freely across the alveoli, but if there is some lung diseases like emphysema, then attainment of equilibrium may be delayed. There will be delay in both induction and recovery.

4. Solubility of drug in blood: This is most important factor responsible for induction as well as recovery of anesthetic agent. Its index is blood-gas partition coefficient (Fig. 11.4.1).

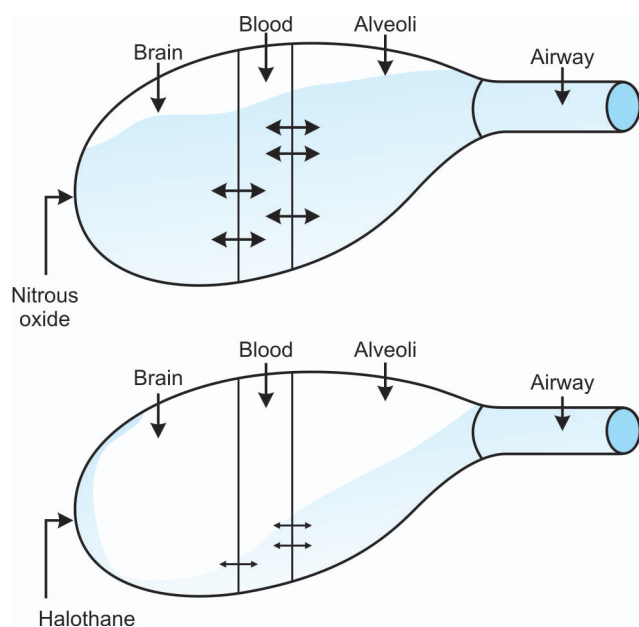


Fig. 11.4.1: Relation between solubility of anesthetic agent and its induction.

- If solubility of the drug is more: there will be less free molecules - there will be less partial pressure - therefore there will be slow rise in the arterial

tension, i.e. slower induction and recovery e.g. halothane

- If solubility of the drug is less: there will be more free molecules of the drug - therefore high partial pressure - there will be quick rise in the arterial tension, i.e. quick induction and recovery e.g. N_2O

5. Pulmonary blood flow (Fig. 11.4.2):

- With increase in cardiac output or pulmonary blood flow there is fall in (blood tension rise), specifically for drugs with higher solubility like halothane, i.e. slower induction.
- With fall in cardiac output or pulmonary flow there is rise in (blood tension rise). Stagnant volume of blood get saturated soon, i.e. faster induction.

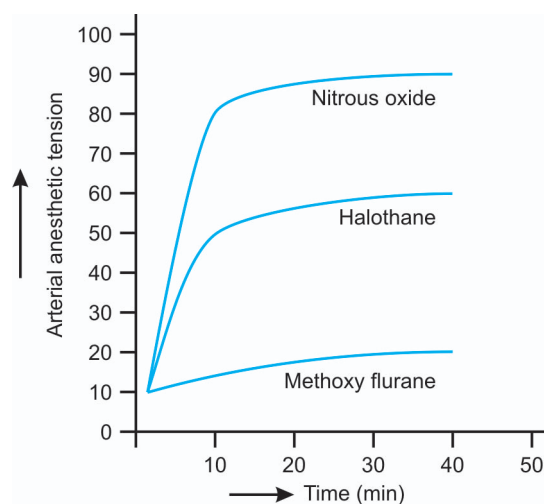


Fig. 11.4.2: Effect of arterial anesthetic tension on induction

6. Solubility of drug in tissue (brain):

- Higher be the tissue solubility, higher be the duration of action of drug.
- If lower be the tissue solubility, lower be the duration of action of anesthetics.

7. Cerebral blood flow:

- If higher be the central blood flow faster be the induction.
- If lower be the central blood flow, induction will be slow.

Pharmacodynamics

Mechanism of action of General Anesthetics

General anesthetics interrupts nervous system functions at various levels including; peripheral sensory nerves, spinal chord, brain stem, and cerebral cortex. But because of diffusely inhibition of electrical activity by anesthetics in CNS, its exact site of action is not known. There are

various proposed theories for mechanism of action of general anesthetics, few of them are:

- **Conformational distortion theory:** Anesthetics after dissolving in membrane lipids increases degree of disorders in their structure by increasing fluidization, i.e. by favoring gel-liquid transition, which secondarily affect membrane bound functional proteins and expand the membrane disproportionately and impedes the ionic flow (decreases Na^+ influx).
- **Meyer overton theory:** According to this the potency of the general anesthetics are directly proportional to lipid solubility of GA.
- **Hydrate or water crystal theory:** According to this theory GA combines with water in the brain and forms ice (microcrystals) which ultimately inhibits nerve functions (probably by impeding neurons and by blocking nerve conduction).
- **Other theories** are also there for example inhibition of glucose metabolism in brain cells, blocking ATP production and by impairing oxygen utilization.
- **Action may be mediated via receptors:**
 - a. By activating or potentiating inhibitory **GABA and Glycine receptors** and
 - b. By inhibiting excitatory glutamate transmitter at **NMDA type receptors**.

Elimination of anesthetics. It occurs in the same way and in the reverse order of induction. Most GAs are eliminated unchanged except halothane which is > 20% metabolized in liver.

CLASSIFICATION

Inhalational anesthetics

- | | |
|----------------------|--|
| A. Gases: | Nitrous oxide (N_2O), Cyclopropane |
| B. Volatile liquids: | Ether, Halothane, Enflurane, Isoflurane, Methoxyflurane, Chloroform (toxic). |

Intravenous anesthetics

- | | |
|-------------------------|--|
| Inducing agents | Thiopentone sodium, Propofol, Etomidate Methohexitone, |
| Dissociative anesthesia | Ketamine |
| Neuroleptanalgesia | [Fentanyl + Droperidol] combination |
| Benzodiazepines | Diazepam, Lorazepam, Midazolam |

Properties of an Ideal Anesthetic Agent

Ideal anesthetic should be pleasant, non-irritating, provide adequate analgesia, immobility and muscle relaxation; should be non-inflammable and administration should be easy and controllable and have a wide margin of safety.

Induction and recovery should be smooth, and not affect cardiovascular functions. It should be inexpensive.

INHALATIONAL ANESTHETICS (Fig. 11.4.3)

Systemic effects of inhaled anesthetics : Effect on

1. Cardiovascular System:

- Majority of GAtics decreases mean arterial pressure either due to reduction in cardiac output or as a result of decrease in systemic vascular resistance.
- They may alter heart rates
 - Halothane: produces bradycardia (vegal stimulation)
 - desflurane/Isoflurane: produces tachycardia (due to sympathetic stimulation)
 - majority of them also increase right arterial pressure.

2. Respiration:

- All inhaled anesthesia produces dose dependent fall in tidal volume and increase in respiratory rate except nitrous oxide.

3. Brain:

- Majority of GAtics decreases metabolic rate of brain. Inhalation anesthetics with higher solubility: reduces vascular resistance therefore increase cerebral blood flow.
- “NO” is least likely to increase cerebral blood flow.
- Halothane, isoflurane and enflurane depresses EEG.

4. Kidney:

- All of them produces, dose dependent effect on fall in GFR and fall in renal blood flow.

5. Liver:

- Inhalational anesthetics also produces dose dependent fall in hepatic blood flow without affecting LFT Liver enzymes.

Nitrous oxide (Laughing gas). It is a gas with a slightly sweetish odor. It produces light anesthesia without significant depression of respiration or vasomotor center.

Advantages

1. Colorless and odorless.
2. It is non-irritating (pleasant induction) and non-inflammable.
3. Strong analgesic
4. Action (Induction) is rapid and smooth
5. Low solubility and rapid recovery.
6. Postoperative nausea is not significant
7. Has little effect on respiration and cardiovascular functions, i.e. heart rate and BP, hence ideal for combination.
8. It is non-toxic to liver, kidney and brain and is quickly removed from lungs.
9. It is cheap.

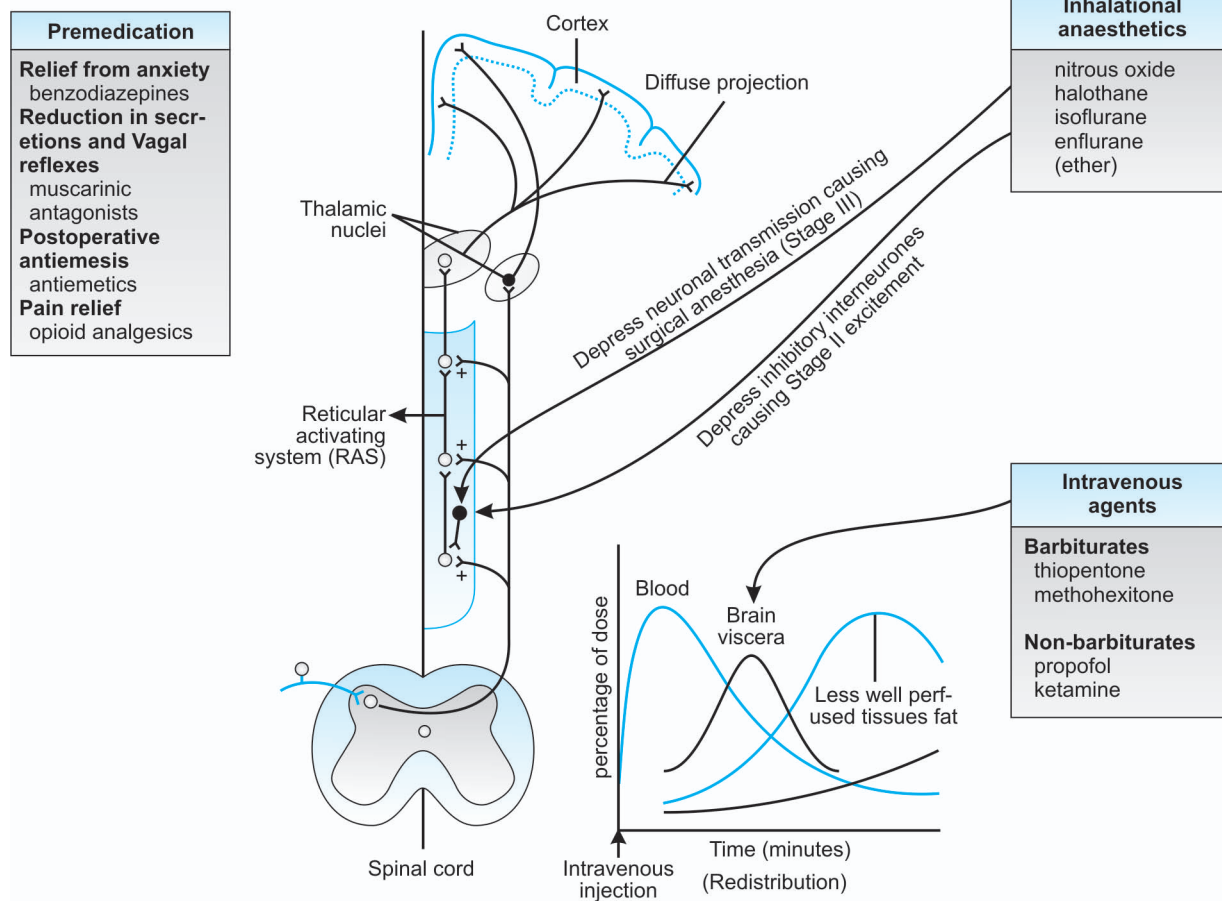


Fig. 11.4.3: General anesthesia

Disadvantages

1. It is less potent and should be used with other agents.
2. Poor muscle relaxant.
3. Second gas effect and diffusion hypoxia occurs with N_2O (laughing gas).
4. No metabolism occurs, it is quickly removed from body by lungs.

Status in anesthesia: Nitrous oxide (70%) is used as an adjuvant with other anesthetics (0.2–2%) along with oxygen (25–30%).

Ether: It is a colorless volatile liquid. It is highly inflammable; vapours are irritating.

Advantages

1. It is cheap and Potent anesthetic agent.
2. Good analgesic.
3. Marked muscle relaxation in deep anesthesia.
4. Effect on cardiovascular and respiratory function are not significant in therapeutic doses; reflexes are well-maintained.
5. Not hepatotoxic

6. It is a bronchodilator.

7. It does not sensitize the heart to adrenaline.

8. Easy to administer as no complicated equipment is required.

Disadvantages

1. Highly volatile liquid, i.e. It is inflammable
2. Diathermy is contraindicated.
3. It is irritating and therefore enhances respiratory secretions. Laryngeal spasm may occur during induction therefore premedication *with atropine* is essential.
4. Highly soluble in body tissues—induction is slow and unpleasant.
5. Recovery is also slow.
6. marked postoperative nausea, vomiting and ratching.

Status in anesthesia: Ether is now not preferred because of inflammability and irritant property. But it is still used in developing countries like India because it is cheap, easy to administer (by open drop method) and relatively safe.

Halothane: It is a colorless volatile liquid with a sweet odor. It is non-irritant and non-inflammable.

Advantages

1. Sweet odor, potent, non-inflammable anesthetic, therefore less dangerous.
2. Non-irritant, therefore does not increase salivary or bronchial secretions.
3. Induction is smooth and moderate slow, i.e. within few minutes surgical anesthesia can be achieved.
4. Recovery is also moderate slow.
5. Pharyngeal and laryngeal reflexes lost therefore no cough.
6. Postoperative nausea and vomiting is of low incidence.

Disadvantages

1. Volatile liquid
2. Expensive.
3. Neither a good analgesic nor a muscle relaxant.
4. Halothane directly inhibits myocardial contractility and therefore decreases heart rate, cardiac output and BP. It also sensitizes the heart to the arrhythmogenic action of adrenaline (tachy-arrhythmias).
5. It also causes respiratory depression.

Side effects: Severe hepatitis and malignant hyperthermia (a genetically determined reaction occurs rarely in few cases which is sometime fatal). Succinylcholine accentuates this effect of halothane. It is due to intracellular release of Ca^{++} from the sarcoplasmic reticulum which causes muscle contraction and increased heat production. It is treated with oxygen inhalation, bicarbonate infusion, external cool sponging and administering IV dantrolene.

Status in anesthesia: Halothane is one of the most popular and preferred anesthetic and it is most widely used.

Enflurane: It is similar to halothane except that:

1. It is metabolized to a lesser extent than halothane—therefore safer regarding the liver toxicity.
2. Recovery is also very pleasant.
3. It decreases heart rate, cardiac output and BP
4. It does not sensitize the heart to adrenaline.
5. Better skeletal muscle relaxant.
6. It has no renal toxicity.

Side effects: It sometimes produces seizures in patients and therefore contraindicated in patients of epilepsy. Very rarely it also causes hepatic necrosis.

Isoflurane: It is an isomer of enflurane and is similar to halothane. It differs as follows:

1. It produces rapid induction and rapid recovery
2. It is more potent than halothane

3. It does not sensitize the heart to adrenaline.
4. It reduces the blood pressure like enflurane but increases the heart rate.
5. It also provokes respiratory secretions.
6. Its metabolism is negligible—therefore safer regarding the liver and renal toxicity
7. It does not provoke seizures

⇒ Isoflurane is extensively used in European Countries. It is expensive.

Desflurane and Sevoflurane

1. These are newer agents which allow very rapid induction and recovery because of low solubility in blood.
2. They are approximately similar to isoflurane in their action. But they too have some disadvantages.
3. Desflurane is pungent: may induce coughing and sometimes laryngospasm.
4. Because of low volatility, a special vapourizer is required for administration.
5. Sevoflurane is chemically unstable. Its metabolite may cause renal damage. If these disadvantages of sevoflurane could be overcome, we may have found an ideal anesthetic.

Methoxyflurane: Slow onset and recovery. It is nephrotoxic.

Clinical uses: Inhalation anesthetics are used in combination with IV anesthetics to maintain anesthesia, as a component of balanced anesthesia nitrous oxide, sevoflurane, desflurane and isoflurane are commonly used. Halothane is used in pediatric anesthesia and in patients with airway problems (asthma) as it is a bronchodilator.

INTRAVENOUS ANESTHETICS (Fig. 11.4.3)

Intravenous anesthetics: These agents are used, both as adjuncts to inhaled anesthetics and as sole agents in short surgical procedures IV Thiopental, etomidate and propofol, have a fast onset of effect and are commonly used for induction of anesthesia. IV opioids provide cardiovascular stability, sedation and so are used for maintenance of anesthesia and to provide anterograde amnesia.

Intravenous anesthetics allow an extremely rapid induction because the blood concentration can be raised rapidly. But there is no channel for quick elimination like the lungs. Moreover, elimination of inhaled anesthetics can be hastened by inducing hyperventilation, while this is not possible with intravenous anesthetics. They get redistributed rapidly in the body tissues. These are used for

induction because of rapid onset of action and anesthesia is maintained by an inhalational agent.

INDUCING AGENTS

Thiopentone sodium:

1. It is an ultrashort-acting barbiturate which is administered parentally.
2. Sometimes extravasations of the solution at the site of injection produces intense pain, necrosis and gangrene.
3. It rapidly induces hypnosis and anesthesia without analgesia.
4. On IV injection (3-5 mg/kg as a 2.5% solution) it produces unconsciousness in 20-30 sec. Its effect remains for 10–20 minutes.
5. It is highly lipid soluble; duration of action is 4-7 minutes.

Advantages: Quick onset of action; induction is smooth, rapid and pleasant.

Disadvantages

1. Not a good analgesic nor muscle relaxant.
2. The required dose for anesthesia results in delay recovery, respiratory (RR) and circulatory (BP) depression therefore it can not be used alone.

Adverse effects

1. A short period of apnea and enhanced respiratory secretions. Laryngospasm may occur.
2. Over dosage results in profound respiratory depression. positive pressure ventilation has to be given.
3. Severe hypotension and hiccoughs may occur.

Propofol

- It is an oily liquid and having short duration of action.
- It produces quick induction (30 sec) and quick recovery (4 min) from a single dose.
- It is used for induction and maintenance for short as well as OPD procedures of up to 1 hour duration. The effect of a single dose is terminated by distribution.
- It can be used for total IV anesthesia as continuous infusion or intermittent injection.
- It is a proconvulsant.

Etomidate: It produces rapid onset and moderately fast recovery. it causes minimal cardiovascular and respiratory depression. It has no analgesic effect and causes a high incidence of nausea and vomiting.

1. It has briefer duration of action (5–10 minutes).
2. It has poor analgesic effect.

3. It produces restlessness and depresses cardiovascular function and respiratory rate.
4. Suppressed production of steroid is not favored.
5. **Like barbiturates:** Rapid onset, pain on injection and reduced cerebral blood flow.
6. **Unlike barbiturates:** Involuntary movements, better cardiovascular stability and less respiratory depression.
7. **Major drawbacks are:** Nausea, vomiting, increased mortality due to suppression of adrenocortical stress response.

Methohexitone is similar to thiopentone but is more potent.

DISSOCIATIVE ANESTHESIA

Ketamine: It causes moderately rapid onset and recovery. It causes dissociative anesthesia characterized by catatonia, amnesia and analgesia without actual loss of consciousness. It is the only anesthetic that produces cardiovascular stimulation : heart rate, blood pressure and cardiac output are increased. It is a useful anesthetic agent for high risk, geriatric patients and patients in shock. It causes “emergence phenomenon” during recovery, which is associated with disorientation, sensory and perceptual illusions and vivid dreams.

Advantages

- Provides profound analgesia and can be used as the sole agent for minor procedures
- Respiration is not depressed, does not induce hypotension
- Pharyngeal and laryngeal reflexes are only slightly affected, i.e. not abolishes.
- Less likely to induce vomiting
- It is of particular value in children and poor-risk patients and also in asthmatic patients since it does not induce bronchospasm.

Disadvantages

- May be dangerous in hypertensives as it raise the BP by enhancing cardiac output and heart rate.
- Hallucination and involuntary movements may occur during recovery if used as a sole agent

Contraindications: Hypertension, CCF, cerebral hemorrhage, increased intracranial tension, psychiatric disorders and pregnancy before term.

Precautions: Pulse and BP should be closely monitored; during recovery patients must be undisturbed and under observation.

NEUROLEPTIC ANALGESIA

A combination of fentanyl and droperidol is used to produce neuroleptanalgesia.

Fentanyl: It is a short-acting (30-50 min) and potent opioid analgesic, related to pethidine

Droperidol

1. It is a, potent, and rapidly acting neuroleptic anti-psychotic related to haloperidol.
2. When the combination is given IV, a state of neuroleptanalgesia is produced. This is characterized by quiescence, psychic indifference and intense analgesia without loss of consciousness. It lasts for 30-40 min.
3. Fentanyl (0.05 mg + droperidol 2.5 mg/ml) 4 to 6 ml is infused IV over 10 min. Patient become drowsy but cooperative. Respiratory depression is present. There is a slight fall in BP and HR (vagal stimulation).
4. During recovery EPS may be seen—due to droperidol. It is indicated and suitable for endoscopies, burn dressing, angiographies and other diagnostic and minor surgical procedures.
5. **Neuroleptanesthesia:** Addition of 65% N₂O + 35% O₂ to the above combination produces neuroleptanesthesia.

BENZODIAZEPINES

Benzodiazepines: Midazolam, lorazepam and diazepam are used, their onset of effect is slow and recovery is also slow, they cause anterograde amnesia. ($T_{1/2}$ = 15-20 min.)

- They are used as a preanesthetic medication, for **intra-operative sedation** and with other drugs as a part of balanced anesthesia.
- BZD may be employed alone in procedures like endoscopies, reduction of fractures, cardiac catheterization and cardioversion. IV midazolam is particularly preferred as it is faster and shorter-acting, more potent and does not cause pain or irritation at injection sites.
- BZDs are also used for induction and maintenance of anesthesia.
- **In conservative dentistry:** Nitrous oxide + Oxygen + Diazepam combination is very popular.

Inhalation Anesthetics

Anesthetic	Advantages
Halothane	Nonflammable Potent Nonirritating

Enflurane	Little change in pulse or respiratory rate Smooth adjustments of depth of anesthesia are possible Adequate skeletal muscle relaxant
Isoflurane	Depth of anesthesia can be rapidly adjusted Cardiac output sustained; arrhythmias uncommon Potentiates action of skeletal muscle relaxants
Desflurane	Very rapid induction and recovery Organ toxicity is negligible
Nitrous oxide	Nonflammable Nonirritating Rapid onset and recovery Little toxicity
Diethyl ether	Good skeletal muscle relaxant

PREANESTHETIC MEDICATION

Preanesthetic medication: This is given prior to the administration of the main anesthetic agent in order to

- a. Relieve pre-procedural anxiety,
- b. Relieve pre-operative pain,
- c. Potentiate the degree of analgesia, and also produces amnesia
- d. Reduce the side effects of the anesthetic agent used,
- e. Reduce the quantity of the anesthetic agent required
- f. Reduce bronchial secretion, bradycardia and
- g. Reduce the incidence of post-operative vomiting, and also reduce Gastroesophageal reflex.

The drugs used for this purpose are:

- a. Sedatives and anxiolytics—diazepam, lorazepam, nitrazepam.
 - b. Antiemetic drugs—promethazine, chlorpromazine
 - c. Analgesics—morphine, fentanyl, pethidine.
 - d. Anticholinergics—atropine, hyoscine, glycopyrrolate—these are used to reduce secretions and prevent cardiac arrest during induction of anesthesia.
 - e. H₂ receptor blocking agents—ranitidine, roxatidine—these are used to reduce gastric acid secretion and prevent aspiration of gastric contents.
- A. Preanesthetic medications can facilitate an uncomplicated anesthetic and operative course by improving the rapidity and smoothness of induction, reducing anxiety, providing analgesia and amnesia, and compensating

for the salivation, bradycardia, and other side effects of anesthesia.

1. **Sedative hypnotics:** Tranquilizers, such as diazepam, are useful in a wide variety of anaesthetic situations. They can provide preoperative sedation, help to prevent and treat the CNS stimulation caused by local anesthetics, and provide amnesia. Barbiturates, such as secobarbital and pentobarbital, are the preoperative sedatives most frequently employed. These agents produce less postoperative nausea and vomiting than opioids.
2. **Opioids**, such as morphine, fentanyl, and alfentanil, often are given to patients who are to be anesthetized with general anesthetics of fairly low potency, such as the combination of nitrous oxide and thiopental. In addition, they can be administered with a barbiturate or diazepam for regional anesthesia. In both instances, they provide analgesia. Alfentanil may offer advantages over fentanyl for longer procedures. Response and recovery appear to be more rapid.
3. **Phenothiazine derivatives, such as promethazine** and the antihistamine hydroxyzine, often are administered concomitantly with opioids because they

potentiate the analgesic effects without increasing the side effects.

4. **Anticholinergic agents:** They are used to
 - reduce the secretions
 - prevent bradycardia due to vagal stimulation
 - prevent laryngospasm which is due to excessive secretions.
- Atropine and scopolamine, as well as the quaternary ammonium compound glycopyrrolate, are used routinely to decrease the flow of saliva. Because of a lower incidence of undesirable side effects, glycopyrrolate is recommended as the anticholinergic agent of choice for bronchoscopy.
- B. **Drugs that reduce acidity:** H_2 blockers like ranitidine decrease gastric acid secretion and are given on the night before surgery. Decrease in gastric secretions reduces the damage to lungs if aspiration occurs while on anesthesia.
- C. **Gastrokinetic agents:** Metoclopramide is a dopamine antagonist that promotes gastrointestinal motility and increase the tone of esophageal end of the stomach. This speeds gastric emptying. The combination of H_2 blocker + metoclopramide provides best protection against aspiration.

Sedative Hypnotics

Sedative (Anxiolytic) Agents

- They reduce anxiety (reduces excitement)
- Increases or produces calming (quietening) effect without inducing sleep.
- Reduces responsiveness to any level of the stimulation

Note: CNS depression is minimum.

Hypnotics

- Facilitate onset and maintenance of sleep state which is equivalent to natural sleep
- They produce drowsiness.

Note: CNS depression is pronounced (maximum).

Hypnotic state may be produced by using sedative in higher doses. It is totally different from “Hypnosis” : trans like state.

- **Anesthesia** : Reversible loss of consciousness.
- **Coma** : Irreversible loss of consciousness.

SLEEP

Definition: It is an active, circadian, physiological depression of consciousness. It is determined by central pacemakers with (biological clock) which are situated in suprachiasmatic nuclei of the hypothalamus.

- All human beings need sleep. Insomnia is sleeplessness.
- Normal sleep consists of distinct stages based on 3 physiological measures
 - **EEG** (Electro-encephalogram): It records brain waves.
 - **EMG** (Electromyogram)
 - **ENG** (Electro-nystagmogram): It measures the lateral movement of the eyeball.
- Sleep can be classified into two types depending on above physiological characteristics (measures).

1. NREM (Non-rapid eye movement) sleep: Also called as **Orthodox sleep**.

→ **NREM** sleep divided into 4 stages (1 to 4), they are:

- Stage 0:** Awake (alpha: when eyes closed, beta: when eyes open)
- Stage I:** Dozing (alpha + theta)
- Stage II:** Unequivocal sleep (theta + spindles): K (kappa) or complex present
- Stage III:** Deep sleep transition (alpha, delta and spindles)
- Stage IV:** Cerebral sleep (delta activity) deep sleep. No K complex

[**alpha:** amplitude high and frequency = 8-14 CPS,
beta: amplitude low and frequency = 15-35 CPS,
theta: amplitude low and frequency = 4-7 CPS,
delta: amplitude high and frequency = 0.5-3 CPS]

- * 70 – 75% of total sleep.
- * Thinking is present.
- * HR (Heart rate)/BP (Blood pressure)/RR (Respiratory rate): remains steady or decreases.
- * Muscles relaxed.
- * GH (Growth Hormone) (somatotropin): Maximum released.
- * Night terrors and somnambulism may occur.

2. REM (Rapid eye movement) sleep (Paradoxical sleep):

- * Constitute approximately 20 – 30% of sleep.
- * No K complexes.
- * HR/BP/RR: fluctuates
- * Irregular eye movement present
- * Dreams/nightmares: occurs and can be recalled.
- Throughout the night, NREM and REM sleep cycles repeat alternatively for brief periods. Approximately 1/3rd of our life is spent in sleep.

CLASSIFICATION

1. Benzodiazepines

Long-acting	Diazepam, Flurazepam, chlor-diazepoxide, Chlorazepate.
Short-acting	Lorazepam, Nitrazepam, Temazepam, Triazolam, Midazolam, Clonazepam, Alprazolam

2. Barbiturates

Phenobarbitone, Pentobarbitone, Mephobarbitone, Secobarbitone, Thiopentone, Hexobarbitone

3. Newer agents

Zolpidem, Zopiclone

4. Miscellaneous

Chloral hydrate, Paraldehyde, Glutethimide.

BENZODIAZEPINES (BZD)

- First important member of family BZD: Chlor-diazepoxide was the first to be introduced into clinical medicine in 1961 (accidental discovery in Hoffmans – Roche laboratory).
- Thousands of BZDs have been synthesized of which 20 are important and now in clinical use.

Chemistry

Benzodiazepines

- Benzene ring: 6 C atoms
- Diazepine ring: 7 C atoms
- Chain / ring: (substituent)

Pharmacokinetics

- Pharmacokinetic properties varies from member to member.
- Absorption depends upon lipid solubility. Most of them absorbed from GIT completely (varies). Chlorazepate converted to nordiazepam in stomach and then absorbs.
- Plasma protein binding (PPB) also varies from member to member, i.e PPB is 10% for Flurazepam, while it is 95% for diazepam.
- Distribution: Wide.
- Blood brain barrier (BBB): For high lipid soluble member—**Rapid**, while for low lipid soluble member—**Slow**.

Metabolism

- The member of this group is metabolized in liver by
 - De-alkylation and
 - Hydroxylation.
- The metabolites are active (with higher $T_{1/2}$) as well as inactive.
- Benzodiazepine: participate in **enterohepatic circulation**, and the metabolites are excreted in urine after glucuronoidation

- BDZ crosses placenta as well as it also secretes in the milk.

Classification according to Pharmacokinetic Profile

1. Slow elimination of parent drug or metabolites:

high $T_{1/2}$: Residue effect next morning. Suitable for the patients with high nocturnal awakening). E.g. Flurazepam.

2. Relatively slow elimination but rapid distribution:

E.g. Diazepam, Nitrazepam, Flunitrazepam

3. Relatively rapid elimination with fast distribution: (Low $T_{1/2}$)

E.g. Temazepam

4. Ultra-rapid elimination:

- They are good for sleep induction but poor for maintenance of the sleep.
- They produce rebound effect.
E.g. Triazolam (peak effect: 1 hour), Midazolam (peak effect: 20 minutes)

Pharmacological actions: The most important actions of BZDs are on **CNS** and includes.

Sedation and Hypnosis

- BZDs increase the sleep duration and also hasten ($\uparrow$) the onset of sleep.
- They decrease sleep latency + stage I NREM. It also reduces REM.
- It increases stage II NREM
- The quality of sleep resembles natural sleep compared to other hypnotics.
- Tolerance develops to this effect gradually.
- In lower doses they are sedative and anxiolytic while in higher doses they are hypnotics.
- Respiration is also suppressed (not significantly) but it get precipitated with alcohol.

Anxiolytic: BZDs reduce anxiety and aggression and thus produce a calming effect.

Muscle relaxant action

- BZDs reduce muscle tone which is centrally mediated.
- The muscle relaxation by BZDs adds an beneficial effects in patients of psychosomatic illness because generally anxiety is associated with increased muscle tone and may be responsible for aches and pains in these patients.

Anticonvulsant effects

- BZDs increase the seizure threshold and act as anticonvulsants (antiepileptics).
- Diazepam** is used intravenously for the treatment of *status epilepticus* while
- Clonazepam is used in the treatment of *absence seizure* and *myoclonic seizures* in children.

GIT

- Diazepam reduces nocturnal HCL/Gastric secretion, relieves gastric stress ulcer.
- BZDs also relieves spastic colitis/irritable bowel syndrome.

Site and Mechanism of action: BZDs binds with BZD receptor as shown in Fig. 11.5.1 (which is a GABA receptor-chloride channel complex). The GABA_A-BZD receptor Cl⁻ channel complex is composed of 4-5 subunits, i.e. α , β , γ & δ as shown in figure 11.5.1 and increase the frequency of chloride channel opening (Cl⁻ influx), resulting in hyperpolarization.

BZDs as hypnotics-when compared with barbiturates:

1. BZDs induces sleep which resembles natural sleep with less hangover.
2. BZDs have lower abuse liability.
3. In hypnotic doses they do not affect respiration or cardiovascular functions.
4. BZDs have a higher safety margin (high therapeutic index, approx. = 50x) and are safer than barbiturates even in overdoses. The respiratory depression in over doses is milder. There is no loss of consciousness and amnesia.
5. In case of BZD toxicity, a specific BZD antagonist-flumazenil can be used to reverse the symptoms.
6. BZDs do not cause microsomal enzyme induction and therefore do not alter the blood levels of other drugs.

Because of the above reasons, BZDs are the most preferred sedative hypnotics.

Adverse effects

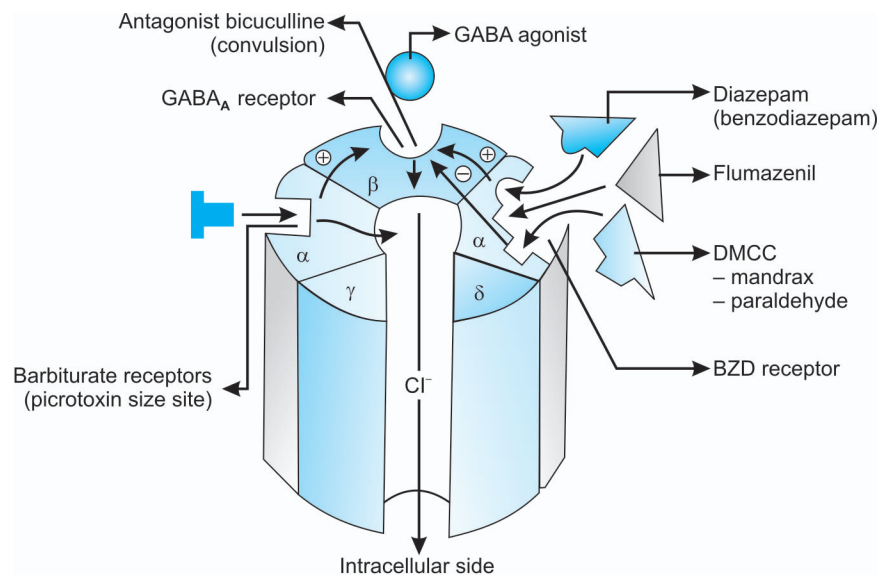
- BZDs are generally well tolerated and are safer.
- The common side effects include dizziness, vertigo, confusion, amnesia, lethargy, ataxia, increased reaction time, and impaired psychomotor skill such as driving - therefore, while on BZDs (therapy) driving should be avoided.
- In some patients BZD's may cause paradoxical irritability and anxiety.
- Weakness, blurring of vision, dry mouth and urinary incontinence may be present.

Tolerance and dependence

- As compared to barbiturates both tolerance and dependence liability are less with BZDs.
- Patients may develop tolerance to the sedative effects of BZDs.
- The withdrawal symptoms are milder and slower in onset because of the longer plasma half-life in most BZDs, they may be abrupt and more intensive with short-acting agents.
- Cross tolerance is present with alcohol and other CNS depressants.

Contraindications

- Pregnancy, Labor, breastfeeding mothers.
- When given to a pregnant mother during labor, BZDs cause hypotonia and respiratory depression in the neonate therefore they are unsafe (**teratogenic**) in pregnant female.



Flumazenil— Competitive antagonist at BDZ-site.
 β carboline (DMCM)— Inverse agonist of BZD site.

Fig. 11.5.1: Mechanism of action

Drug Interactions (not significant)

- Alcohol : It increases BZDs induced CNS depression.
- OCP (Oral Contraceptive Pills) or Cimetidine : Reduces BZDs metabolism

Therapeutic Indications of BZDs

1. **Insomnia:** BZDs are the Drug of choice.
2. **In anxiety states:** For the treatment of anxiety and neuroses BZDs are the Drug of choice.
3. **As anticonvulsants:** IV diazepam is the drug of choice in the treatment of status epilepticus. Clonazepam is used as an adjunct with other anti-epileptic drugs.
4. **Muscle relaxant:** BZDs are centrally acting muscle relaxants in chronic muscle spasm and spasticity.
5. **During alcohol withdrawal:** BZDs are useful during withdrawal of alcohol or other sedative-hypnotics.
6. **As preanesthetic medication** for their sedation and anxiolytic effects.

Flurazepam: It produces hypnotic effects within 20-40 minutes after an oral dose, which may last for 6-8 hours. Flurazepam causes less suppression of REM sleep than other benzodiazepines. Overdosage can occur and is treated as for other benzodiazepines. At moderate dosage, addiction potential is low, as is withdrawal (rebound) insomnia, which is often seen with many of the other hypnotics.

Triazolam: It has the shortest latency period before sleep, but because of its short duration of action, its effects may not persist through the night. It is used for the short-term treatment of insomnia. It is least likely to cause residual drowsiness but may cause day time anxiety. Rebound insomnia may occur.

Temazepam: It is conjugated with glucuronic acid and is excreted in the urine; therefore, hepatic dysfunction has little effect on its elimination. Temazepam decreases awakenings and increases sleep time. It does not affect sleep latency.

Benzodiazepine antagonist**Flumazenil**

- It is a BZD analogue
- It is used parenterally (IV)
- $T_{1/2} = 1$ hr and duration of action 1-2 hrs.
- It abolishes hypnogenic, psychomotor cognitive and EEG effects of BZDs
- Uses:
 - To reverse BZD anesthesia
 - BZD overdose treatment.
- Adverse effects: Agitation, anxiety withdrawal tremors, cremps, etc.

BARBITURATES

- In 1903 barbitone and in 1912 phenobarbitone were discovered by Fischer and Von miring on St. Barbara's days
- Barbiturates were the largest group of hypnotics in clinical use until the 1960s.

Chemistry

- Barbiturates are the derivatives of barbituric acid.
- The parent compound, barbituric acid, is derived from dehydration of urea and malonic acid. Barbituric acid itself has no depressant effect on the CNS.

Classification

Barbiturates are classified on the basis of their onset and duration of action.

- Ultra-short-acting barbiturates** (e.g., thiopental) act within seconds, and their duration of action is 30 minutes.
- Short-acting barbiturates** (e.g., pentobarbital) have a duration of action of about 2 hours; *Its principal use is as sleep-inducing hypnotic. (amytal)*
- Intermediate-acting barbiturates** (e.g., amobarbital) have an effect lasting 3-5 hours. *Their principal use is as hypnotics; (amytal)*
- Long-acting barbiturates** (e.g., phenobarbital) have a duration of action greater than 6 hours. *They are effective hypnotics and sedatives and at low doses are used as antiepileptic agents, but they are likely to cause hangover.*

Pharmacokinetics

- Barbiturates are well-absorbed. They are absorbed from the stomach, small intestine, rectum, and intramuscular sites.
- Distribution: widely distributed in the body. They also redistribute if administered IV.
- Blood Brain Barrier (BBB): Penetration to BBB directly proportional to lipid solubility.
- They readily cross the placental barrier, and concentration in the fetal blood approach those in maternal blood.
- The duration of action of a barbiturate depends on:
 - Its rate of metabolic (hepatic) degradation
 - Its degree of lipid solubility
 - The extent to which it binds to serum proteins, which reduces renal excretion.
- Barbiturates are metabolized in the liver. They are hepatic microsomal enzyme inducers. The metabolites are excreted in urine.

Mechanism of action

- **At low doses**, barbiturates either have γ amino butyric acid (GABA)-like action or enhance the effects of GABA, (an inhibitory neurotransmitter.)

- When GABA receptors are activated, chloride channels open. Chloride enters the cell, hyperpolarizes it, and produces decreased excitation (Fig. 11.5.1).
- **At higher doses,** They directly increases chloride conductance and
- **At very higher doses,** they reduces both calcium and potassium channels.
- There is also a picrotoxin site associated with the GABA receptor to which barbiturates bind. The greater the affinity of a barbiturate for the picrotoxin binding site, the greater is its potency (Fig. 11.5.1).
- Barbiturates are less selective than benzodiazepines, which also have GABA-like action, because elevating the dose of barbiturates produces a generalized CNS depression in addition to selective depression at synaptic sites.
- Barbiturates produce dose-dependent effect, i.e. sedation → sleep → anesthesia → coma → death.

Pharmacological actions

CNS Barbiturates cause depression of all excitable tissues including CNS.

- **Sedation and hypnosis:** In low doses, barbiturates induce sleep and prolong the duration of sleep. The REM-NREM sleep cycle is altered with decreased duration of REM and prolonged NREM sleep. Hangover with headache and residual sedation are the minor side effect after waking up.
- They (barbiturates) reduces anxiety, impair short-term memory and judgment. They can produce euphoria and are drugs of addiction while some people may experience dysphoria. Barbiturates produce hyperalgesia (increased sensitivity to pain). Therefore barbiturates, when given as hypnotics for pain in a patient may be more troublesome than being of any benefit.
- **Anesthesia:** If administered in higher doses barbiturates produce general anesthesia. The ultra short acting barbiturates are used intravenously for this purpose.
- **Anticonvulsant effects:** Barbiturates have anticonvulsant action. Phenobarbitone and mephobarbitone have specific anticonvulsant activity and are used in the treatment of epilepsy.

Respiratory system: Barbiturates depress the respiration. High doses bring about a direct paralysis of the medullary respiratory center.

Cardiovascular system

- Hypnotic doses of barbiturates produce non significant reduction in blood pressure and heart rate.
- Toxic doses of barbiturates produce a significant fall in BP due to vasomotor center depression and direct decrease in myocardial contractility.

Skeletal muscles: Higher doses of barbiturates depress the excitability of the neuromuscular junction.

Other actions

- Most barbiturates, especially phenobarbital, can induce hepatic microsomal drug-metabolizing enzymes. This results in increased degradation of the barbiturate, ultimately leading to barbiturate tolerance.
- It also causes increased inactivation of other compounds, such as the anticoagulants, phenytoin, digitoxin, theophylline, and glucocorticoids, leading to potentially serious problems with drug interactions.
- Barbiturate-induced porphyria can occur as a result of more rapid hemoglobin degradation.

Adverse reactions

- Depressant effects include over sedation and a decrease in REM sleep.
- Hangover-due to residual depression of the CNS may be accompanied by nausea, vomiting, vertigo and diarrhea.
- Hypersensitivity reactions like skin eruptions, porphyrias, swelling of the eyelids and lips and sometimes exfoliative dermatitis can occurs.
- In the presence of respiratory disorders, the hypnotic doses of barbiturates can cause serious respiratory depression.
- Withdrawal of a barbiturate may result in grandmal seizures, severe tremors, vivid hallucinations, and psychoses. Therefore, its abrupt withdrawal should be avoided.

Tolerance and dependance

- On repeated administration, tolerance develops to the effects of barbiturates.
- Development of both **psychological and physical dependence** to barbiturates make them one of the drugs with abuse liability. Withdrawal symptoms include anxiety, restlessness, abdominal cramps, hallucinations, delirium and convulsions.

Acute Barbiturate Poisoning

- The fatal dose of phenobarbitone is 6-10 gm.
- An overdose can result in coma. Manifestations include diminished reflexes (although deep tendon reflexes are usually intact), severe respiratory depression, hypotension leading to cardiovascular collapse, skin eruptions and renal failure.

Treatment: There is no specific antidote. The measures include:

1. Gastric lavage followed by administration of activated charcoal (or universal antidote) to prevent further absorption of barbiturates.

- General supportive measures like; maintenance of BP, adequate oxygen administration and positive pressure ventilation.
- Forced alkaline diuresis with sodium bicarbonate, a diuretic and IV fluids will hasten the excretion of long-acting barbiturates through the kidneys since they are acidic drugs
- Hemodialysis or peritoneal dialysis is useful and often needed.

Therapeutic uses (Indications): Although barbiturates are still used as sedative-hypnotic agents, They are being replaced for this purpose by the benzodiazepines because of the following disadvantages.

- They have a narrow, i.e. therapeutic range. ($\downarrow$ T.I.)
 - They suppress REM sleep.
 - Tolerance develops relatively quickly.
 - They have a high potential for physical dependence and abuse.
- Sedation and hypnosis:** Benzodiazepines are preferred to barbiturates as sedative hypnotics.
 - Anesthesia:** Thiopentone sodium is used IV for the induction of general anesthesia.
 - Peanesthetic medication:** Barbiturates were used earlier for the sedative-hypnotic property, but are not preferred now.
 - Antiepileptic:** Due to their rapid onset of action, barbiturates (i.e. Phenobarbital, pentobarbital, amobarbital, thiopental) are used in the emergency treatment of convulsions as in status epilepticus. In adults, however, the benzodiazepines are the drugs of choice.
 - Neonatal jaundice and kernicterus:** Phenobarbitone is a microsomal enzyme inducer and thereby enhances the production of glucuronyl transferase-the enzymes required for metabolism and excretion of bilirubin. It therefore help in the clearance of jaundice in the neonates.
 - Barbiturates, especially in anesthetic doses, significantly decrease oxygen utilization by the brain, which may be of value in lessening cerebral edema caused by surgery or trauma and in protecting against cerebral infarction during **cerebral ischemia**.

NONBARBITURATE SEDATIVE HYPNOTICS

CHLORAL HYDRATE: It is used as an alternative to BZD. It has a bad taste and is an irritant causes nausea and vomiting. It produces hypnosis without affecting respiratory and cardiovascular functions. Not preferred now.

Pharmacokinetics

- Chloral hydrate is metabolized in the liver by alcohol dehydrogenase to trichloroethanol, which is a active metabolite producing the CNS effects.

- Trichloroethanol and, to a lesser extent, chloral hydrate are oxidized to trichloroacetic acid, which is excreted in the kidney, as the glucuronide conjugate.

Therapeutic uses

- Chloral hydrate is a relatively safe hypnotic drug, inducing sleep in a half hour and lasting about 6 hours. It causes a relatively small reduction in REM sleep.
- It is used mainly in children and the elderly and is most effective when used for 2-3 nights to treat transient insomnia.

Adverse effects

- Chloral hydrate is bad-tasting and irritating to the gastrointestinal tract.
- The CNS depressant effects are potentiated by alcohol (the combination being dubbed a “Mickey Finn”).

PARALDEHYDE: It is a colorless, transparent, pungent, inflammable liquid. It is an irritant and can dissolve plastic therefore can not be given by plastic syringe. It can be given rectally, intramuscularly and orally.

Chemistry: Paraldehyde is a trimer of acetaldehyde.

Mechanism of action

- Paraldehyde produces hypnosis in about 15 minutes, and its effects last 4-8 hours.
- Its CNS depressant activity resembles that of alcohol, chloral hydrate, and the barbiturates.

Route of administration: Paraldehyde can be administered orally, parenterally, or rectally.

Therapeutic uses

- Paraldehyde is used exclusively for patients undergoing withdrawal from alcohol.
- It is used for patients with hepatic or renal failure because it is mainly eliminated via the lungs.

Adverse effects

- Its strong odor and disagreeable taste limit its use mainly to hospitals.
- It is a gastrointestinal irritant.
- It should not be used with disulfiram.

NEWER AGENTS

Zolpidem: It is a newly developed hypnotic-non-benzodiazepine drug. It is claimed to be a better hypnotic. Adverse effects are similar to BZD.

Zopiclone: It is another new hypnotic. Its actions resemble those of BZDs.

Zaleplon: Strongest among three. oral bioavailability 25-30% and $T_{1/2} = 1$ hr, therefore can be taken in night without causing morning sedation and rebound insomnia.

Antiepileptics

Epilepsy: “Disease of Lightning” [Mirgi] correctly described by JH Jackson, 100 years back.

Definition: Group of disorder of CNS characterized by:

- *Paroxysmal cerebral dysrhythmia,*
- *Brief episodes of seizures (loss or disturbance of consciousness)*
- *With or without convulsions (characterized body movement)*
- *Sensory or psychiatric phenomenon.*

Nature of Epilepsy

- Epilepsy is a common neurological abnormality that affects about 0.5-1 % of the population
- The characteristic event is the seizure, which is often associated with convulsions, but may occur in many other forms.
- The seizure is caused by an abnormal high-frequency discharge of a group of neurons, starting locally and spreading to a varying extent to affect other parts of the brain.
- The symptoms (classification) of the epilepsy depends upon
 - a. The site of primary discharge and
 - b. The extent of its (discharge) spread.
- Seizures may be partial or generalized depending on the location and spread of the abnormal neuronal discharge. The attack may involve mainly motor, sensory or behavioral phenomena. Unconsciousness occurs when the reticular formation is involved.
- Repeated epileptic discharge can cause neuronal death (excitotoxicity).
- Current drug therapy is effective in 70-80% of patients.

Classification of Epilepsy

- The particular symptoms produced depends on the function of the region of brain that involves/affected, i.e.

- a. Involvement of Reticular formation in brain stem:- Loss of consciousness (seizures)
- b. Involvement of motor cortex: Convulsions.
- c. Involvement of hypothalamus:- Peripheral autonomic discharge

Seizures have been classified into generalized and partial seizures.

GENERALIZED SEIZURES

- Account for 30%-40% of all epilepsies.
- It involve the whole brain including reticular system (i.e. brain stem). There occur production of abnormal electrical activity throughout both hemisphere therefore immediate loss of consciousness. It may be:

Generalized tonic-clonic seizures (Grand mal, GTC or Major epilepsy)

- It is characterized by Aura → Cry → Unconsciousness:
 - a. **Tonic phase:** Strong contraction of muscles throughout the body (rigid extensor spasm), lasting for 1 minute and then, *[Decrease in respiratory rate, micturation, defecation, salivation, etc.]*
 - b. **Clonic phase:** A series of violent synchronous jerks, i.e periods of muscle contraction alternating with periods of relaxation (convulsions) lasting for 2-4 minutes followed by
 - c. **CNS depression:** The person goes into prolong deep sleep. Injury may occur during the convulsive episode.

Absence seizures (minor or petitmal epilepsy)

- It is more important in children.
- In this, there is sudden and brief loss of consciousness.
- Patient apparently freezes, stop working or speaking in between, stares in one direction.

- There is mild clonic jerking of eyelids or extremities, small chewing movement of mouth and automatism. The episode lasts for a brief period usually less than 30 seconds.
- (n= 2.4–100/day) and EEG shows: 3 cycles/second spike

Myoclonic seizures

- It involve a sudden, brief, shock like momentary contraction of muscles.
- It may be limited to a part of the body (limb) or may affect the whole body.
- There is characteristic EEG changes.
- It may present itself alone or may coexist with other type of seizures.

Atonic/Akinetic seizures (Drop attacks)

- It is characterized by sudden loss of postural tone for a few seconds and the person may drop to the ground without any tonic-clonic movement.
- Head drop may be present.
- It usually reflects: *Diffuse brain damage*.

Infantile Spasm

- It occurs in the infants and is not a form of epilepsy
- There occurs intermittent, sudden muscle spasm (flexion and extension of the body and limbs)
- It is usually associated with mental retardation, kernicterous, hypoglycemia and infection.

PARTIAL SEIZURES

- It account for about 60% of all epilepsies.
- In this category of seizures discharge begins locally in the cortex and often remains localized.
- There is no impairment of consciousness (RAS intact) and also no effect on mood and behavior.

Simple partial seizures (Cortical focal epilepsy)

- There is no impairment of consciousness.
- It is often secondary.
- The manifestation depends on the site (area involved) in the cortex; motor (convulsion of that part), sensory (parasthesia), olfactory, auditory and psychological symptoms (fear, anger, etc.)
- Convulsions are confined to a group of muscles, i.e. if the motor cortex representing the left thumb is involved, there is recurrent contractions of the left thumb.
- This type of seizures lasts for 20-60 seconds.

Complex partial seizures. (CPS, temporal lobe epilepsy, psychomotor epilepsy)

- Aura is present.
- Seizure focus: temporal lobe.

- This is characterized by confused behavior (bizarre), purposeless movements like lip-smacking, hand wringing or swallowing and emotional changes lasts for 30 sec to 2 minutes.
- Impairment of consciousness may be present.

Partial with secondarily generalized seizures (Secondary Generalized)

- Simple or complex partial seizure may evolve into a generalized seizure.
- Partial seizures followed by general tonic clonic seizures
- Orderly march seizures (if present): Jacksonian seizures.

STATUS EPILEPTICUS: It is the continuous clinical manifestation of an epileptic discharge without intermission:

- Prolong seizure: duration more than 5–10 minutes.
- Repetitive seizures: without recovery of consciousness between attacks.
- If generalized tonic clonic seizure: It is an emergent condition: may be lethal.

OTHER DISEASES/DISORDERS RESEMBLES EPILEPSY

- | | |
|------------------------|------------------------------|
| 1. Febrile convulsions | 6. Sleeping disorders |
| 2. Vertigo | 7. Eclampsia/Pre-eclampsia |
| 3. Syncope | 8. Hypoglycemia |
| 4. Drop attack | 9. Transient ischemic attack |
| 5. Necrolepsy | 10. Posthypotensive episode |

ETIOLOGICAL AND PRECIPITATING FACTORS

1. Family history: 30%.
2. Trauma (head injury) and surgery:
 - Sub-arachnoid hemorrhage
 - Medial temporal sclerosis
 - Instrumental (forceps) delivery
 - Surgery of cerebral hemisphere
3. Pyrexia: Temperature > 104°F (at an age < 5 years): Leads to febrile convulsions
4. Intracranial mass (tumor)
5. Cerebral infarction.
6. Drug induced/Drug withdrawal induced: *Phenothiazines, MAO inhibitors, TCA antidepressants, Amphetamine, Lignocaine, Nalidixic acid, etc.*

In higher doses these drugs produces seizures specially in low threshold persons.

- Alcoholics: They are susceptible, even alcohol induced hypoglycemia sensitized the person toward seizures.
- Withdrawal from anticonvulsants specifically phenobarbitone

7. Encephalitis and other inflammatory condition of the brain
8. Metabolic abnormalities Like: Hypocalcemia, Hypoglycemia, Hyponatremia, Acute hypoxia, Hepatic failure, Uremia, etc.
9. Degenerative brain disorders like; Alzheimer's disease
10. Photosensitive and other type of reflex epilepsies.

INVESTIGATIONS

1. EEG (Electro-encephalography): Cortical spike wave: (Grand Mal Epilepsy).
2. EEG (Electro-encephalography): 3 Hz spike wave (petit mal epilepsy)
3. EEG (Electro-encephalography): Telemetry
4. CT scanning/MRI

EXPERIMENTAL ANIMAL MODELS FOR EVALUATING ANTIEPILEPTIC DRUGS

- Many animal models have been devised, including electrically and chemically induced generalized seizures, production of local chemical damage, and kindling. These provide good prediction of antiepileptic drug effects in humans.
- 1. **Kindling:** Brief burst of weak and low intensity electrical stimulation (impulses) intermittently applied to the brain (specially to amygdala) produces **GTC** like seizures.
- 2. **Leptazol (PTZ):** Pentylene tetrazole, leptazole and cardizole injection produces clonic convulsions. Drugs antagonizes this convulsions are useful in assessment of patitmal epilepsy.
- 3. **Maximal Electroshock Seizure:** Brief high intensity shock, when applied to head of mice produces GTC seizures.
 - Drugs used to treat epilepsies: Antiepileptic drugs
 - Drug used to treat convulsions: Anticonvulsants (muscle relaxants).

NEUROPHYSIOLOGY OF EPILEPSY

- John H Jackson—first define epilepsy
- Characteristic pathophysiological event is the PDS (paroxysmal depolarization shift) of neuronal membrane and burst discharge.
- Normally EAA (excitatory amino acid), e.g. Aspartate and Glutamate initiate seizures discharge while GABA (gamma amino butyric acid) terminate seizures. Therefore, epilepsy is due to either higher concentration of EAA or reduced concentration of GABA.
- Factors which triggers the epileptically incidence area are: alkalosis, hypoglycemia, over hydration, hypocalcemia, overeating strong emotions, i.e. fear.

Mechanism of action of antiepileptic drugs (Fig. 11.6.1)

- The neurochemical basis of the abnormal discharge is not well understood. It may be associated with enhanced excitatory amino acid transmission, impaired inhibitory transmission, or abnormal electrical properties of the affected cells. The glutamate content in areas surrounding an epileptic focus is often raised.
- Current antiepileptic drugs are thought to act mainly by two main mechanisms:
 - Reducing electrical excitability of cell membranes, possibly through blocking voltage dependent sodium channels.
 - Enhancing GABA-mediated synaptic inhibition. This may be achieved by an enhance postsynaptic action of GABA, by inhibiting GABA-transaminase, or by drugs with direct GABA-agonist properties.
- A few drugs appear to act by a third mechanism, namely inhibition of T type calcium channels (Fig. 11.6.2).
- Newer drugs act by other mechanisms, yet to be find out.
- Drugs that block excitatory amino acid receptors are effective in animal models, but not yet developed for clinical use.

CLASSIFICATION OF ANTIEPILEPTIC DRUGS (Fig. 11.6.2)

Hydantoins	Phenytoin sodium, Mephenytoin
Barbiturates	Phenobarbitone, Mephobarbitone
Deoxybarbiturate	Primidone
Iminostilbene	Carbamazepine
Succinimide	Ethosuximide, Methsuximide
GABA transaminase inhibitors	Sodium Valproate, Vigabatrin
GABA re-uptake inhibitor	Tiagabine
GABA agonist	Gabapentin
Benzodiazepines	Diazepam, Clonazepam, Lorazepam, Clobazam
Miscellaneous	Gabapentin, Lamotrigine, Acetazolamide,
Newer	Tiagabine, Gabapentin, Lamotrigine Vigabatrin, etc. Topiramate, Levetiracetam

The major antiepileptic drugs: The main drugs in current use are: phenytoin, carbamazepine, valproate and ethosuximide.

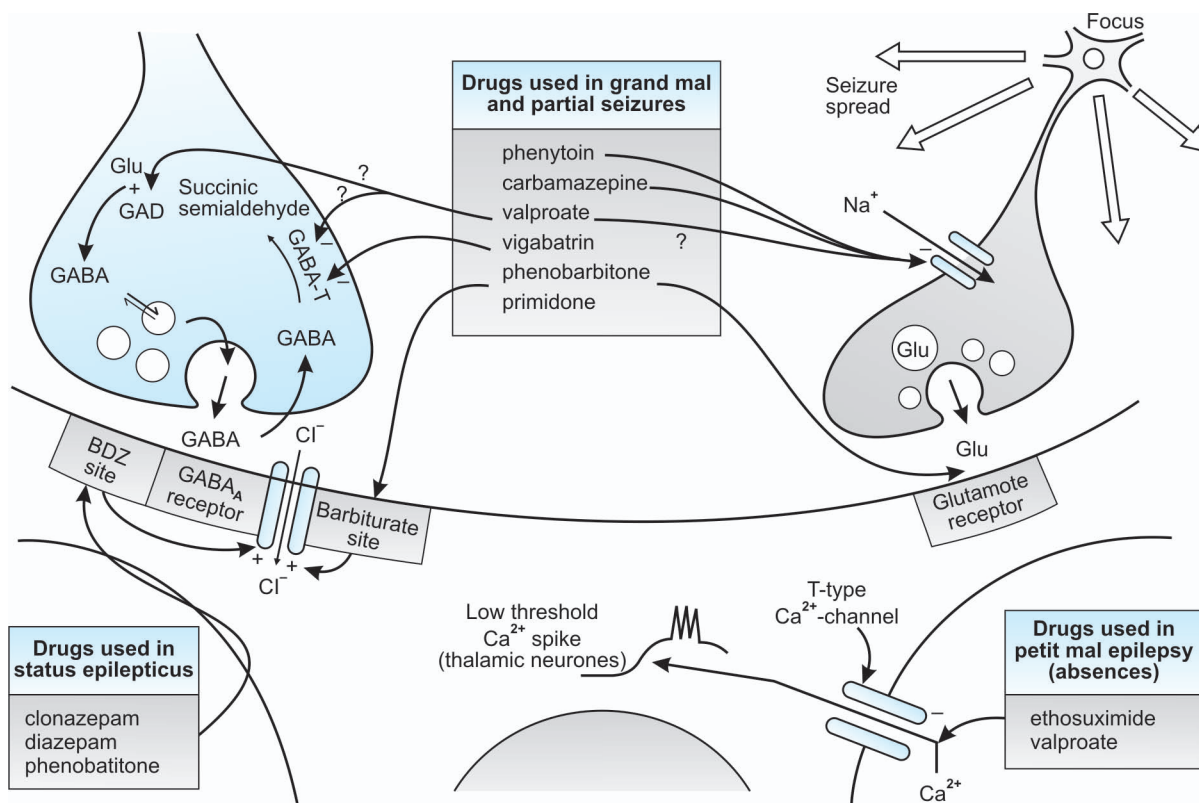


Fig. 11.6.1: Mechanism of actions of antiepileptic drugs

DIPHENYL-HYDANTOIN (PHENYTOIN SODIUM)

- It was synthesized in 1908.
- Its anticonvulsant property was discovered only in 1938.
- It is a barbiturate analogus.

Pharmacokinetics

- Phenytoin is poorly water-soluble hence slow oral absorption.
- 80%-90% bound to plasma proteins.
- Wide distribution.
- It is metabolized in the liver initially by **first order** and **later by zero order kinetics** as the dose increases.
- Plasma Monitoring is useful.
- It is an enzyme inducer.

Pharmacological Actions

CNS: It exerts antiseizure activity without causing general depression of the CNS.

Mechanism of action

- Phenytoin stabilizes the neuronal membrane (local anesthesia like effect) by blocking voltage dependent sodium channels.

- It inhibits the generation of repetitive action potentials.
- Calcium influx during depolarization also reduced.
- It also reduces PDS (paroxysmal depolarization shift).
- It also increases GABA and 5HT level.

Adverse effects depend on dose, duration and route of administration.

1. Nausea, vomiting, epigastric pain, anorexia.
2. Nystagmus and diplopia are common.
3. **Gingival hyperplasia** is more common in children on prolonged use.
4. **Endocrinal:**
 - **Hirsutism**, acne, coarsening of facial features.
 - **Hyperglycemia** (phenytoin inhibits insulin release).
 - **Osteomalacia**,
 - **Hypersensitivity:** rashes, hepatic necrosis, lymphadenopathy, etc.
5. **Megaloblastic anemia**
6. **Teratogenicity:** If taken by the pregnant lady, It produces **fetal hydantoin syndrome** characterized by

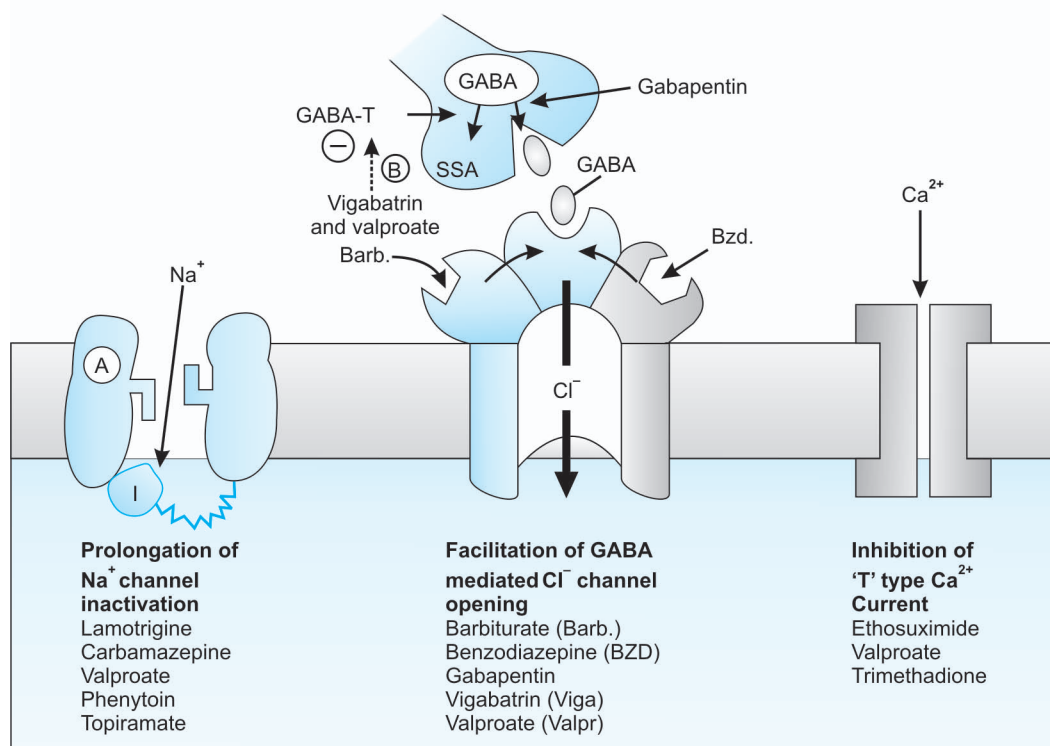


Fig. 11.6.2: Mechanisms of actions of majority of antiepileptic drugs

A: Activation gate; I: Inactivation gate; GABA-T: GABA transaminase; SSA: Succinic semialdehyde

hypoplastic phalanges, cleft palate, harelip and microcephaly in the offspring.

Dose related toxicity

- Cerebral manifestations: Ataxia, vertigo peripheral neuropathy, etc.
- Behavioral alteration: Confusion, hallucination, etc.

Drug interactions

- Phenytoin is an enzyme inducer, i.e. it induces microsomal enzymes and increases degradation of other drugs: failure of OCP (Oral Contraceptive Pills), digitoxin, theophylline, etc.
- If given with Phenobarbitone or Carbamazepine, phenytoin enhance each others metabolism.
- Valproate increases plasma phenytoin level.
- Cimetidine and chloramphenicol inhibit the metabolism of phenytoin resulting in toxicity.

Therapeutic Indications

- 1. Grandmal epilepsy:** Generalized tonic-clonic seizure and partial seizures (not useful in absence seizures): 100 mg BD
- 2. Status epilepticus:** Phenytoin is used by slow IV injection.
- 3. Psychomotor seizures**

4. Trigeminal neuralgia: Alternative to carbamazepines.

5. Cardiac arrhythmias: Phenytoin is sometime useful in digitalis induced arrhythmias.

PHENOBARBITONE

- Phenobarbitone was first introduced in 1912.
- It was the first effective antiepileptic drug, and still remains one of the widely used drugs.
- **Advantages:** Well tolerated, $t_{1/2}$ long, and it is cheaper.

Pharmacokinetics

- Slow but complete oral absorption.
- $t_{1/2}$ long: 80–120 hours.
- Metabolized in Liver and excreted by kidney.
- It is also a microsomal enzyme inducer.

Antiepileptic actions

- Primidone: It is the precursor of phenobarbitone which is rarely used now.
- Phenobarbitone has specific anti-epileptic activity and raises the seizure threshold.

Mechanism of action

- Barbiturates, not only depresses the CNS but also enhances the inhibitory neurotransmission in the CNS.

by enhancing the activation of GABA receptors and thus;

- It also possesses GABA facilitatory, GABA mimetic and antigitamate action

Therapeutic indications: Phenobarbitone is one of the widely used antiepileptics because of its efficacy and low cost. It is used in:

1. Grandmal epilepsy: Generalized tonic-clonic seizures (3–6 mg/kg/day)
2. Status epilepticus
3. Partial seizures.

CARBAMAZEPINE

- It was first introduced in 1960.
- Carbamazepine is a tricyclic compound, structure resembles to imipramine.

Antiseizure activity

- Carbamazepine has good anti-seizure activity. Its mechanism of action is similar to phenytoin, i.e. it blocks sodium channels. (Figure 11.6.2)
- Carbamazepine is also useful in the treatment of trigeminal neuralgia (severe pain along the distribution of the trigeminal nerve) and glossopharyngeal neuralgia.
- Carbamazepine is also found to be beneficial in mood disorders.

Pharmacokinetics

- Slow oral absorption.
- 75% bound to plasma protein.
- It has a $t_{1/2}$ of 10–20 hours.
- Metabolized in liver.
- It is also a microsomal enzyme inducer.

Similar profile to that of phenytoin, but with fewer unwanted effects

Adverse effects

- Nausea, vomiting and dizziness are common.
- **Neurotoxicity:** Drowsiness, vertigo, ataxia, diplopia, blurring of vision, mental disturbances may occur.
- **Hypersensitivity reactions:** like skin rashes may occur.
- **Hematological toxicity:** includes leucopenia, thrombocytopenia and rarely agranulocytosis and aplastic anemia.
- Water retention.
- It is teratogenic.

Therapeutic indications

- Effective in most forms of epilepsy (except absence seizures);

- Psychomotor epilepsy: (temporal lobe epilepsy)
- Generalized tonic clonic seizures (grand mal epilepsy).
- Simple and complex partial seizures.
- Trigeminal neuralgia and glossopharyngeal neuralgia: **carbamazepine is the drug of choice.**
- **Bipolar mood disorder:** Carbamazepine is used as an alternative to other antidepressants.

SUCCINIMIDES: ETHOSUXIMIDE. The main drug used to treat absence seizures, may exacerbate other forms

- Ethosuximide is the primary agent for absence seizures.
- It raises the seizure threshold.

Pharmacokinetics

- Completely absorbed from GIT
- 20% excreted unchanged in urine.
- Rest is metabolized in the liver.

Mechanism of action: Ethosuximide reduces or blocks the low threshold calcium currents (T currents) in thalamic neurons.

Adverse effects

- The most common adverse effects are **nausea, vomiting**, epigastric pain, gastric irritation and anorexia which can be avoided by starting with a low dose and gradually increasing it.
- **CNS** effects like drowsiness, euphoria, dizziness, headache and hiccough
- **Hypersensitivity** reactions like rashes, urticaria, leucopenia have been reported.

Uses: Ethosuximide is the drug of choice for **absence seizures**.

VALPROIC ACID (Sodium Valproate). Chemically unrelated to other antiepileptic drugs

- Valproic acid (salt: sodium valproate): It is effective in many types of epilepsies including **absence seizures, partial and generalized tonic-clonic seizures**.

Pharmacokinetics

- Oral absorption is good
- 90% bound to plasma protein.
- $t_{1/2}$: 15 to 20 hours.

Mechanism of action

1. It enhances the level of inhibitory amino acid: GABA by:
 - increased synthesis of GABA
 - decreased metabolism of GABA.
2. By blocking the sodium channels like phenytoin.
3. Decreasing the brain level of excitatory amino acid.

Adverse effects

- Well tolerated in Indian patients.
- **Anoraxia, vomiting, and epigastric** distress occur initially.
- Rashes and thrombocytopenia.
- **Fulminating hepatitis**—though rare can be fatal.
- Monitoring of liver functions are mandatory.
- Valproic acid is **teratogenic**, it can cause neural tube defects.
- Tremors, sedation, ataxia, rashes and alopecia are rare.

Therapeutic indications

- Useful in partial **PATITMAL** and generalized seizures.
- Valproic acid is particularly useful in absence seizures (Akinetic epilepsy)

BENZODIAZEPINES (discussed in sedative hypnotics)

- Benzodiazepines have useful anticonvulsant properties.
- Diazepam is the drug of choice in **status epilepticus**.
- **Clonazepam**: is useful in both absence and myoclonic seizures. But tolerance may develop to its antiepileptic effects.
- **Clobazam**: It is effective in most types of epilepsies and it is less sedative.

New antiepileptic drugs

- **Vigabatrin**
 - Acts by inhibiting GABA-transaminase therefore increasing brain GABA.
 - Effective in patients unresponsive to conventional drugs
 - Main side-effects: drowsiness, behavioral and mood changes
- **Lamotrigine**
 - Acts by inhibiting sodium channels
 - Broad therapeutic profile (spectrum)
 - Main side-effects are hypersensitivity reactions (specially skin rashes)
- **Felbamate**
 - Mechanisms of action unknown
 - Broad therapeutic profile (spectrum)
 - Use limited to intractable cases, owing to risk of severe hypersensitivity reactions
- **Gabapentin**
 - Mechanism of action is not known
 - Saturable absorption, therefore safe in overdose
 - Relatively free of side-effects.
- **Tiagabine**
 - GABA uptake inhibitor
 - Side-effects are dizziness and confusion
 - Not yet fully evaluated

• **Topiramate**

- Complex actions, not fully understood
- Similar to phenytoin with fewer side-effects and simpler pharmacokinetics
- Risk of teratogenesis

TREATMENT OF EPILEPSIES (Fig. 11.6.3)

- An attempt should be made to detect the cause of epilepsy.
- When drugs are found to be necessary, the goal of therapy is to keep the patient free of seizures without interfering with normal daily activity.
- Treatment should be started with a single drug at a low dose; dosage is increased gradually, preferably by monitoring the drug levels in plasma
- If a single drug is not effective, another drug should be tried.
- Good compliance is very important for success.
- **Regarding the duration:** Decision should be made on an individual basis and dose should be very gradually reduced over months to avoid **status epilepticus**.

Clinical uses of antiepileptic drugs

- **Tonic-clonic (grand mal) seizures:** **Carbamazepine** (preferred because of low incidence of side-effects), **phenytoin, valproate:** Use of single drug is preferred when possible, because of risk of pharmacokinetic interactions. Newer agents (not yet fully assessed) include **vigabatrin, lamotrigine, felbamate, gabapentin**.
- **Partial (focal) seizures:** **Carbamazepine, valproate, clonazepam** or **phenytoin** are alternative.
- **Absence seizures (petit mal):** **Ethosuximide** or **valproate**. Valproate is used when absence seizures coexist with tonic-clonic seizures, since most drugs used for tonic-clonic seizures may worsen absence seizures.
- **Myoclonic seizures:** **Valproate** or **clonazepam**.
- **Status epilepticus;** must be treated as an emergency, with diazepam intravenously or (in infants with no accessible veins : rectally.)

Febrile convulsions

- 2–5% of children experience convulsions during fever (hyperpyrexia); of them 2–3 percent become epileptics.
- Children < 18 months developing febrile convulsions, those with neurological abnormalities and those with seizures lasting for > 15 minutes, those with complex seizures—all these have greater risk of recurrence.

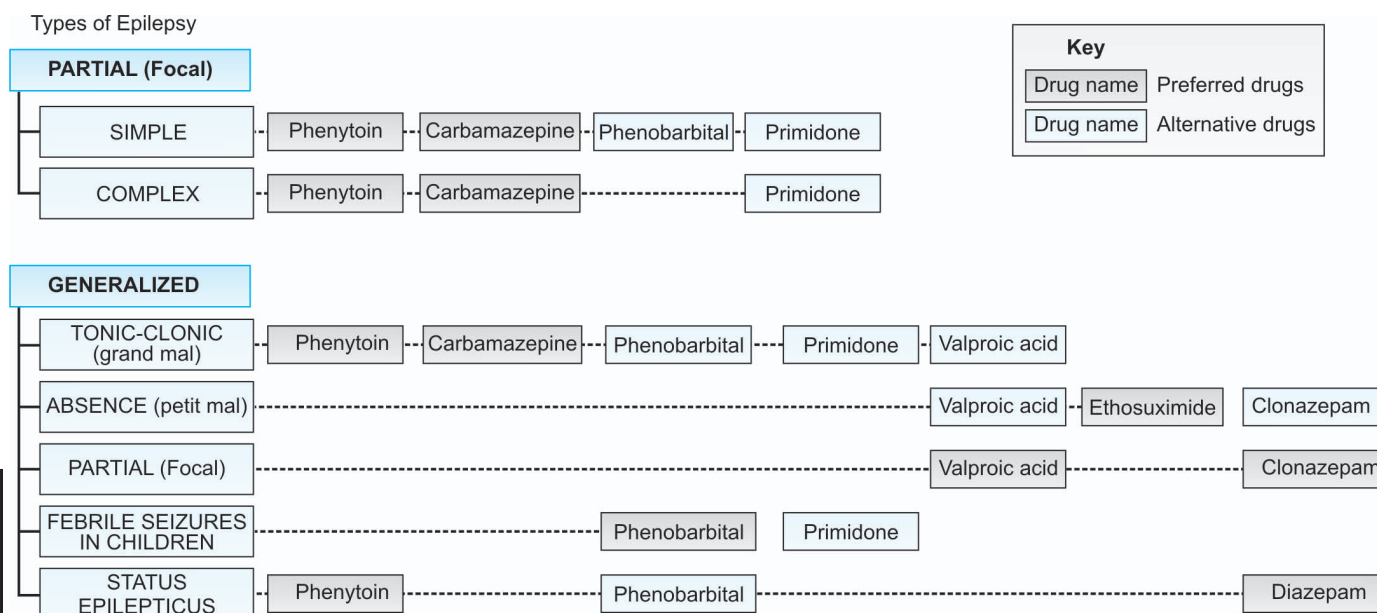


Fig. 11.6.3: Therapeutic indications for anticonvulsant agents

- **Prophylaxis and treatment:** Every attempt should be made to see that they do not develop fever but when they do the temperature should not be allowed to rise by using paracetamol and external cooling. **Diazepam** (0.5 mg/kg given orally or rectally) at the onset of fever prevents convulsions, diazepam rectally or intravenously can be used for treatment.

STATUS EPILEPTICUS (Fig. 11.6.3)

It is an emergent condition which may be fatal if not treated properly.

1. **Diazepam:** 10 mg IV every 10-15 minutes up to 30 mg is the **drug of choice** or **Clonazepam:** 1-2 mg IV is an alternative drug.
2. **Phenobarbitone:** 100-200 mg IM/IV, or **Phenytoin:** 25 mg/min IV maximum up to 1 gram.
3. **Paraldehyde:** 5-10 ml deep IM or 16 ml rectal

- Some prefer to combine **diazepam and phenytoin** (60 mg/min).
- *If seizures continue (not responding):* **General anesthesia** is the last resort.
- Airway maintenance (positive pressure ventilation) is important. Other measures like oxygen, fluid and electrolyte maintenance, monitoring of BP and cardiac rhythm is essential.
- After the control of seizures, long-term antiepileptic therapy is required.

Epilepsy During Pregnancy

- Antiepileptics should be continued because abrupt discontinuation increases the risk of status epilepticus which is hazardous to the fetus.
- Add any non teratogenic drug with previous drug, then only stop the established drug in tapering fashion.

Antianxiety Drugs (Anxiolytics), Antidepressants and Mood Stabilizers

Definition

Anxiety is tension or apprehension which is a normal response to certain situations in life. It is a universal human emotion. But when it becomes excessive and disproportionate to the situation, it becomes disabling and needs treatment.

Measurement of anxiolytic activity

- Behavioral tests in animals are based on measurement of the behavioral inhibition (considered to reflect 'anxiety') in response to conflict or novelty.
- Human tests for anxiolytic drugs employ psychiatric rating scales or measures of autonomic responses, such as that galvanic skin response.
- Tests such as these can distinguish between anxiolytic drugs (benzodiazepines, 5-HT agonists, etc.) and other types of psychotropic drug.

AGENTS USED IN THE TREATMENT OF ANXIETY (Fig. 11.7.1)

Classification

- **Benzodiazepines:** The most important class, used for treating both anxiety states and insomnia. *Examples* are Diazepam, Chlordiazepoxide, Lorazepam, Alprazolam
- **5-HT_{1A}-receptor agonists:** Recently introduced, showing anxiolytic activity with little sedation. Buspirone, Gepirone, Ipsapirone
- **Barbiturates:** Now largely obsolete as anxiolytic/sedative agents, though still occasionally prescribed. *Example:* Phenobarbitone
- **β -adrenoceptor antagonists:** Used mainly to reduce physical symptoms of anxiety (tremor, palpitations, etc.); no effect on affective component, e.g. Propranolol.
- Miscellaneous other agents are still used occasionally to treat insomnia (benzodiazepines are preferable in most cases) and Meprobamate, Hydroxyzine, etc.

General considerations: Unlike the antipsychotic agents, these agents are used to treat anxiety or neurosis. They are not used in the treatment of psychosis. These drugs, therefore, are known as anti-anxiety agents or minor tranquilizers.

- Antianxiety agents have sedative and hypnotic properties and possess some central skeletal muscle relaxant activity.
- They have a habituation and physical dependence liability.
- Generally, the antianxiety agents have a lower incidence of adverse effects than the antipsychotic agents.

Meprobamate: It is a propyl alcohol derivative (propanediol carbamate). At one time, meprobamate was a widely used anti-anxiety agent; however, it has largely been replaced by the benzodiazepines.

Pharmacokinetics

- Meprobamate is well absorbed from the gastrointestinal tract, and its peak serum concentration is reached in about 11/2 hours.
- Metabolism occurs in the liver, and the inactive metabolites are excreted via the kidney.

Pharmacological effects

- Meprobamate depresses the CNS in a fashion similar to that of the barbiturates, especially phenobarbital, but meprobamate is shorter acting.
- It is capable of promoting sleep, but, like phenobarbital, it decreases the REM phase.
- The skeletal muscle relaxant activity demonstrated by meprobamate is probably a combination of its sedative effect and specific central skeletal muscle relaxant activity.

Adverse effects

- Drowsiness, often seen with full therapeutic doses.
- Blood dyscrasias, including purpura, but these are rare
- Habituation and physical dependence with long-term administration (withdrawal from drug therapy should, therefore, be gradual)

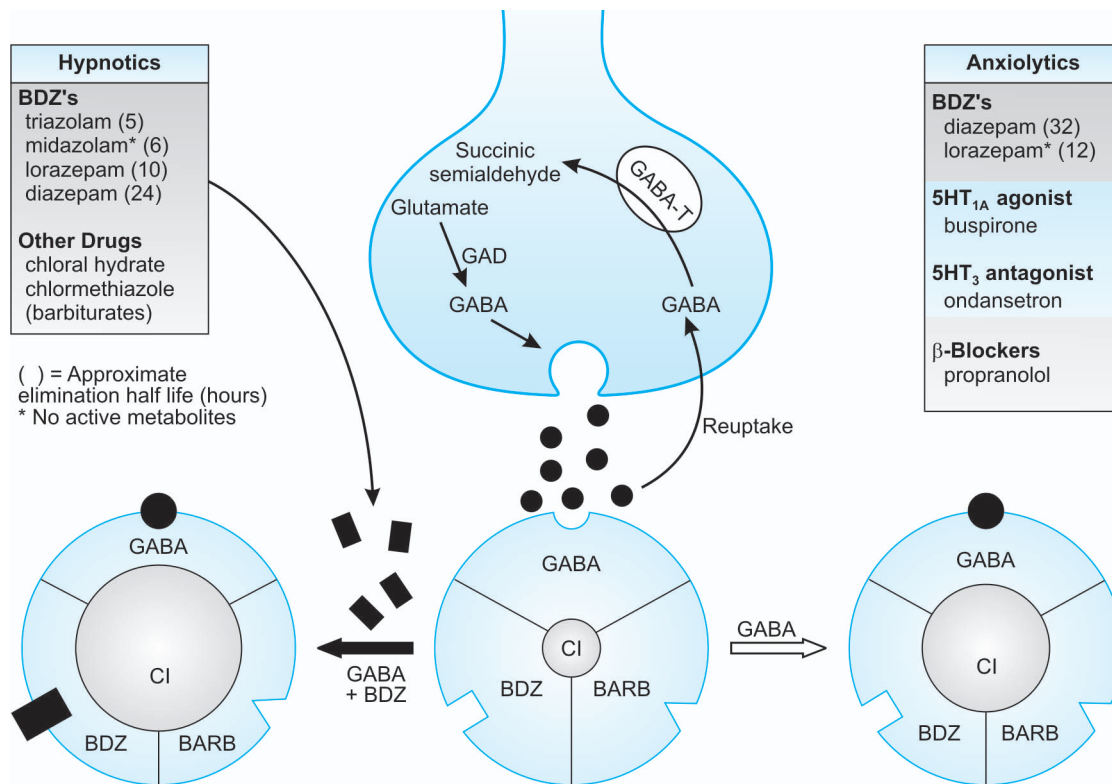


Fig. 11.7.1: Anxiolytics and hypnotics (BARB = Barbiturate)

Benzodiazepines: They are considered the drugs of choice in the treatment of anxiety, partly because of their high therapeutic index. The first benzodiazepine developed was chlordiazepoxide. Others include diazepam, clonazepam, lorazepam, oxazepam, flurazepam, triazolam, and temazepam

Pharmacokinetics

- Diazepam, flurazepam, and clonazepam are relatively rapidly absorbed, while oxazepam, prazepam, and temazepam are more slowly absorbed. Triazolam, midazolam, alprazolam, and clonazepam have an intermediate onset of action.
- All benzodiazepines are soluble in lipids and cross the blood-brain barrier. Plasma levels reflect brain levels.
- Benzodiazepines are metabolized primarily by microsomal oxidation and glucuronide conjugation.

Pharmacological effects

- **CNS effects**
 - Benzodiazepines potentiate the binding of GABA to receptors. The benzodiazepine receptor that helps to potentiate the GABA binding is as yet unidentified.

- Because they increase the seizure threshold, benzodiazepines are useful as anticonvulsants, especially diazepam in status epilepticus. They prevent convulsions caused by strychnine or pentylene-terazole.
- Benzodiazepines are also effective hypnotics, and flurazepam, temazepam, and triazolam are promoted as such.

- At therapeutic doses, the benzodiazepines have minimal effects on the **cardiovascular system**.
- Although the benzodiazepines, especially diazepam, are widely used as central skeletal muscle relaxants, their effectiveness has not been firmly established.

Therapeutic uses

- Treatment of anxiety
- Anesthetic premedication (midazolam is a parenteral benzodiazepine that will replace diazepam for perioperative use; its advantages include less tissue irritation, faster onset of action, and more rapid elimination)
- Use as amnestics, such as in cardioversion
- Use as sedative-hypnotics
- Management of seizure disorders
- Treatment of alcohol withdrawal syndromes

- Use as central skeletal muscle relaxants
- Treatment of night terrors
- Panic attacks (alprazolam only; physical dependence can occur).

Adverse effects

- Adverse effects are partially age- and dose-dependent. These effects include:
 - Ataxia, drowsiness, and sedation (additive depressant effects are seen when benzodiazepines are combined with other agents possessing CNS depressant activity)
 - Paradoxically increased anxiety, including psychoses, especially with high doses
 - Reversible confusion in the elderly
 - Menstrual irregularities, including anovulation
- Overdoses although frequent, are seldom fatal. Treatment is supportive. Owing to the high plasma-protein-binding characteristics of benzodiazepines, the benefit from dialysis is limited.
- Withdrawal symptoms are influenza-like muscle aches and nausea. These symptoms are rare, except in the case of alprazolam.
- Agent-specific effects include:
 - Triazolam may cause rebound insomnia.
 - Lorazepam and triazolam have a greater risk of inducing anterograde amnesia.
 - Flurazepam at higher doses (30 mg) is associated with day time residual sedation.

Pharmacokinetics of Benzodiazepines

Agent	Duration of action	GIT	Active	Half-life period
Midazolam	Short	Intermediate	No	2.5 hours
Triazolam	Short	Intermediate	No	3 hours
Alprazolam	Intermediate	Intermediate	No	14 hours
Lorazepam	Intermediate	Intermediate	No	15 hours
Oxazepam	Intermediate	Slow	No	10 hours
Temazepam	Intermediate	Slow	No	15 hours
Chlordiazepoxide	Long	Intermediate	Yes	2-4 days
Clonazepam	Long	Intermediate	Yes	2-3 days
Clorazepate	Long	Rapid	Yes	2-4 days
Diazepam	Long	Rapid	Yes	2-4 days
Flurazepam	Long	Intermediate	Yes	2-3 days
Halazepam	Long	Slow	Yes	2-4 days
Prazepam	Long	Slow	Yes	2-4 days

Buspirone: It is an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative-anxiolytic drugs.

Mechanism of action

- Although the exact mechanism of action is unknown, buspirone can bind to dopamine and serotonin receptors. It does not bind to benzodiazepine receptors and does not have muscle-relaxant, anticonvulsant, or hypnotic activity.

Pharmacokinetics

- Buspirone is rapidly and completely absorbed from the gastrointestinal tract.
- The drug undergoes an extensive first-pass effect. One hydroxylated metabolite is pharmacologically active.
- Buspirone is highly protein-bound.
- It is partly excreted in the urine and has an elimination half-life of 4.8 hours.

Therapeutic indications

- Buspirone is used for the short-term treatment of generalized anxiety.
- It may require 1-2 weeks for a therapeutic effect to take place.

Adverse effects

- It includes restlessness and dysphoria with high doses.
- Buspirone is remarkably free of other adverse effects. It has little potential for abuse.

β -blockers

- In patients with prominent autonomic sympathetic symptoms of anxiety like tremors, palpitation and hypertension, propranolol may be useful.
- β -blockers are also useful in anxiety inducing states like public speaking and stage performance.
- They can be used as adjuvants to benzodiazepines.

Hydroxyzine: It is an antihistaminic with anxiolytic actions. But due to high sedation it is not preferred.

ANTIDEPRESSANTS (Fig. 11.7.2)

Affective disorders: They are a group of psychoses associated with changes of mood, i.e. depression and mania.

Depression: It is a common psychiatric disorder and could be:

1. *Reactive:* Due to distressing circumstances in life.
2. *Endogenous:* Major depression due to a biochemical abnormality in the brain.
3. *Bipolar mood disorder:* Mania and depression occur alternately causing cyclic mood swings.

Endogenous depression is thought to be due to deficiency of monoamine activity (NA, 5-HT) in the CNS.

Monoamine theory of depression

- The monoamine theory, proposed in 1965, suggests that depression results from functionally deficient monoaminergic (noradrenaline and/or 5-HT) transmission in the CNS.
- The theory was based on the ability of known antidepressant drugs (TCA and MAOI) to facilitate monoaminergic transmission, and of drugs such as reserpine to cause depression.
- Other pharmacological evidence fails to support the monoamine hypothesis.
- Biochemical studies on depressed patients do not, in general, support the monoamine hypothesis in its simple form.
- An abnormally weak response of plasma cortisol exogenous steroid (dexamethasone suppression test) is common in depression, and may reflect defective monoamine transmission in the hypothalamus.
- Though the monoamine hypothesis in its simple form is no longer appropriate as an explanation of depression, pharmacological manipulation of monoamine transmission remains the most successful therapeutic approach.

Testing of antidepressant drugs

- Animal models of depression include:
 - learned helplessness model
 - reversal of reserpine-induced behavioral syndrome
 - mother-infant separation in primates
 None is a good model for human depressive illness, but they are the best available for testing new drugs
- Biochemical and pharmacological measures include inhibition of monoamine uptake, receptor-blocking activity, and enhancement of peripheral noradrenergic transmission.
- Clinical testing of antidepressant drugs necessitates allowance for large placebo effects.

- TCA act by inhibiting uptake of noradrenaline and/or 5-HT by monoaminergic nerve terminals, thus actually facilitating transmission.
- MAOI inhibit one or both forms of brain MAO, thus increasing the cytosolic stores of noradrenaline, dopamine and 5-HT in nerve terminals. Inhibition of Type A MAO correlates with antidepressant activity. Selective Type A MAOI have recently been introduced.
- Atypical antidepressants act by various mechanisms, often poorly understood.
- All types of antidepressant drug take at least 2 weeks to produce any beneficial effects, even though their pharmacological effects are produced immediately, suggesting that secondary adaptive changes are important.
- The most consistent adaptive change seen with different types of antidepressant drugs is down-regulation of β - and α_2 -adrenoceptors, as well as 5HT₂-receptors. How this is related to therapeutic effect is not clear.

Drug Used in Affective Disorders**Classification (See Figure 11.7.2)**

1. *Tricyclic antidepressants (TCA):* Imipramine, Desipramine, Amitriptyline, Doxepin.
2. *Selective serotonin (5-HT) reuptake inhibitors (SSRI):* Fluoxetine, Fluvoxamine, Paroxetine.
3. *Monoamine oxidase (MAO) inhibitors:* Phenelzine, Tranylcypromine, Moclobemide, Clorgyline
4. *Atypical antidepressants:* Trazodone, Bupropion, Mianserine.

TCA → Tricyclic antidepressants

5HT → 5-Hydroxy tryptamine

MAOI → Mono-amine oxidase inhibitors

SSRI → Selective serotonin reuptake inhibitors.

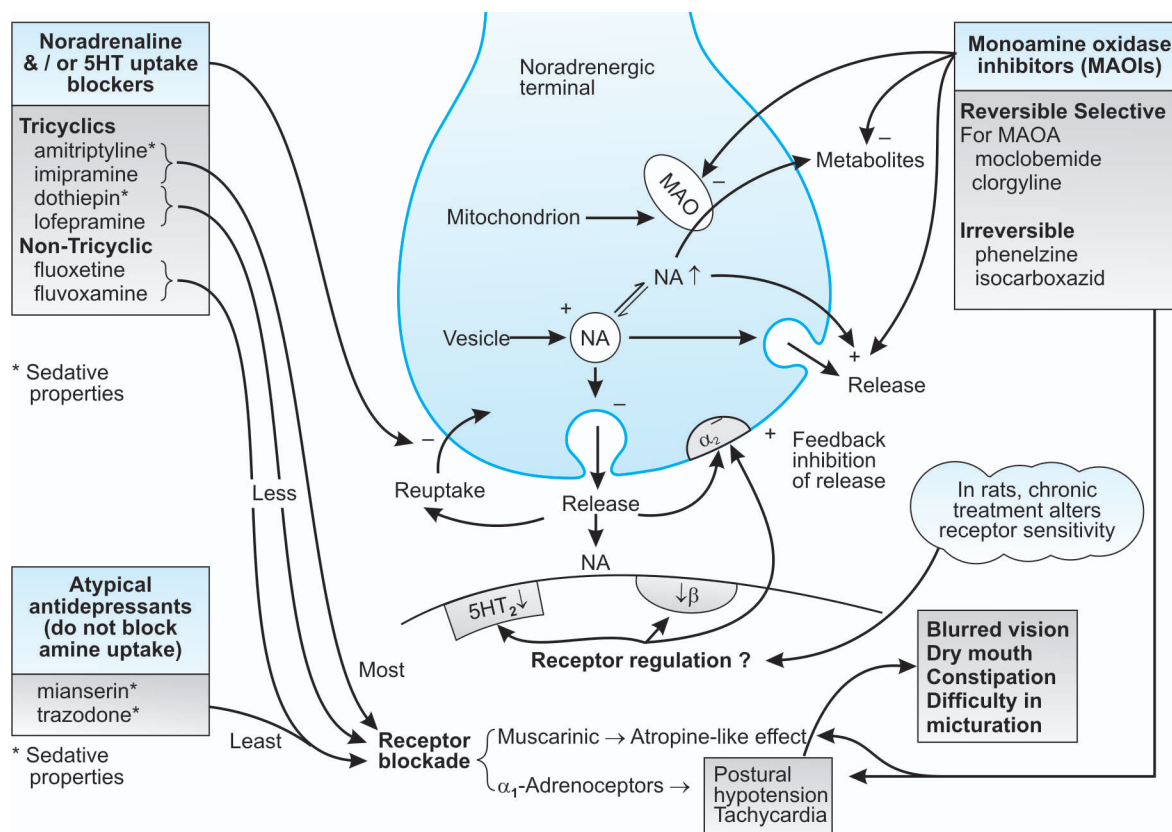


Fig. 11.7.2: Drug used in affective disorders—antidepressants

Antidepressant agents

General considerations

1. Depression is an alteration of mood characterized by sadness, worry, and anxiety. The patient may suffer from losses of weight and libido.
2. Most antidepressants are believed to improve mood by increasing catecholamine stores, although there may be a co-relation between improvement in mood and a decrease in adenylate cyclase.
3. There are various pharmacological modalities that may be useful, and selection often depends on the patient's history and symptoms.

Monoamine Oxidase Inhibitors

Chemistry: Chemically, the MAO inhibitors consist of two major groups, the **hydrazides** and the **nonhydrazides** both are irreversible inhibitors

1. The hydrazide derivatives include isocarboxazid, phenelzine, and iproniazid. The latter is no longer used because of its hepatotoxicity.
2. The prototypic nonhydrazide is tranylcypromine, which structurally resembles dextroamphetamine.

3. Recently reversible inhibitors of MAO-A are included in this group, i.e. Moclobemide and clorgyline.

Pharmacokinetics

- All MAO inhibitors are rapidly absorbed from the gastrointestinal tract, but, inexplicably, the observed therapeutic response does not occur for 2-3 weeks.
- The hydrazide derivatives are cleaved, resulting in biologically active products. Inactivation occurs by acetylation, and, in patients who are genetically slow acetylators, conventional doses of agents, such as phenelzine, may produce exaggerated effects.
- Enzyme regeneration terminates the drug effect, but this frequently takes weeks after use of the drug is stopped.
- When switching antidepressant therapy, a minimum of 2 weeks' delay is required after termination of MAO-inhibitor therapy.

Mechanism of action

- The MAO inhibition forms stable complexes with the enzyme MAO, irreversibly inactivating it, thereby preventing the oxidative deamination of biogenic amines,

such as norepinephrine, epinephrine, dopamine, serotonin, and tyramine.

1. These biogenic amines are, thus, increased significantly in the brain, intestine, heart, and blood.
 2. The increase of biogenic amine levels in the brain is thought to produce the observed antidepressant effects.
- The two types of MAO inhibitors are distinguished by differing responses to specific inhibitors and by differing preferences for substrates.
 1. Type A deaminates serotonin and norepinephrine but not phenylethylamine.
 2. Type B deaminates phenylethylamine better than serotonin or norepinephrine, and it is inhibited by deprenyl. MAO-B is the type found largely in the CNS.
 - The nonhydrazide, tranylcypromine, by way of its amphetamine-like action, releases nor epinephrine centrally.
 - This probably accounts for the relative rapidity of action with tranylcypromine (action can occur in 48 hours) in contrast to the other MAO inhibitors, which have latency periods of 2-3 week.

Pharmacological effects

CNS effects

- a. Besides their effect on depression, MAO inhibitors are effective in sleep disorders, including narcolepsy. They suppress REM sleep.
- b. Except for tranylcypromine, which has a stimulant effect on the electroencephalogram (EEG), other MAO inhibitors have minimal EEG effects.

Cardiovascular effects

- Hypotension, especially postural, can result from the ability of MAO inhibitors to affect ganglionic transmission and reduce the release of norepinephrine in certain organ systems. This effect is believed to be due to the uptake and release of “false transmitters” such as tyramine.
- MAO inhibitors can interact with foods containing high tyramine content, such as cheese, beer, and chicken liver, (**cheese reaction**).
 - The high concentrations of tyramine absorbed from these foods cannot undergo oxidative deamination.
 - The tyramine can, therefore, induce the release of large amounts of stored catecholamines from nerve terminals. This can precipitate a hypertensive crisis, which is the most serious adverse effects of MAO inhibitors.

Hepatic effects

- MAO inhibitors interfere with the detoxification of many drugs.

- They enhance the action of general anesthetics, sedatives, atropine-like agents, narcotics (especially meperidine, which can result in hyperpyrexia), and tricyclic antidepressants.

Therapeutic uses

- MAO-A inhibitors are especially effective in the treatment of atypical depression, characterized by symptoms such as hyperphagia, and hyperanxiety.
- Deprenyl is an MAO-B inhibitor, which may be useful in the treatment of Parkinson’s disease.

Adverse effects

- The most serious effect is marked hypertension from an interaction between an MAO-A inhibitor and certain amines or their precursors.
- Hydrazide-derived MAO inhibitors can cause hepatocellular damage.
- Excessive CNS stimulation has occurred, resulting in insomnia and convulsions.
- Over dosage can result in agitation, headache, hallucinations, convulsions, and hypotension or hypertension. Treatment of over dosage is usually supportive. Since the effects of MAO inhibitors are lengthy, patients should be observed in the hospital for at least 1 week.

Tricyclic antidepressants

Chemistry: Chemically, the tricyclic antidepressants and their desmethyl derivatives are similar to the phenothiazines.

Specific agents

- **Imipramine:** is closely relate to the phenothiazines.
- **Amitriptyline:** is thought to be better tolerated than imipramine in older psychotic or depressed patients. Amitriptyline is effective in multiple sclerosis patients with pseudobulbar palsy, the syndrome of pathological laughing and weeping.
- **Desipramine:** the monodesmethyl derivative of imipramine, is less sedative than its parent compound.
- **Nortriptyline:** like desipramine. produces less sedation than its parent compound amitriptyline.
- **Doxepin:** is also effective in treating depression when anxiety is present.
- **Protriptyline:** has a 3 to 5 day half-life and causes little sedation.

Pharmacokinetics

- The tricyclic antidepressants are well absorbed from the gastrointestinal tract.

- Because of their lipophilic nature, these agents become widely distributed and have relatively long half-lives. They are metabolized in the microsomal metabolizing system. Hydroxylation, N-demethylation, and conjugation with glucuronic acid are the major metabolic pathways.
- The demethylated metabolites of both amitriptyline and imipramine have antidepressant activity.
- Excretion of metabolites is via the kidney.

Mechanism of action

- Tricyclic antidepressants potentiate the action of biogenic amines, presumably by blocking the inactivating reuptake of the amines after release from the presynaptic neuron. It is thought that the demethylated antidepressants (secondary amines) are more selective in blocking the uptake of norepinephrine.
- Tricyclic antidepressants have both antihistaminic (H_1 -receptor - blocking) and α -adrenergic properties.
- In addition, the tricyclic antidepressants possess antimuscarinic action and block the reuptake of serotonin. Tertiary amines (imipramine, amitriptyline) are more effective at blocking serotonin (5HT) uptake.

Pharmacological effects

CNS effects

- A nondepressed person experiences sleepiness when a tricyclic antidepressant is administered. In addition, anxiety and toxic anticholinergic effects may be experienced.
- In the depressed patient, an elevation of mood occurs 2-3 weeks after administration begins. The latency period can be as long as 4 weeks.
- Tricyclic antidepressants can cause extrapyramidal symptoms and ataxia.
- High doses of tricyclic antidepressants are capable of producing seizures and coma.

Cardiovascular effects

- Orthostatic hypotension and arrhythmias are two common effects.
- Tachycardia in response to the hypotension and interference with atrioventricular conduction similar to that produced by quinidine can occur.

The most common **autonomic nervous system** effect is **anticholinergic**. Amitriptyline possesses the most potent antimuscarinic effects.

Therapeutic uses

- These agents are considered the treatment of choice for severe endogenous depression (characterized by regression and inactivity). In terms of overall efficacy, the

various tricyclic antidepressants are equivalent at appropriate dosages.

- Enuresis (**bed wetting**) has been successfully treated with imipramine.
- Obsessive – compulsive neurosis accompanied by depression, and phobic anxiety syndromes, chronic pain, and neuralgia may respond to tricyclic agents; it should be noted that these indications are investigational.

Adverse effects

- The adverse effects of tricyclic antidepressants often resemble those seen with phenothiazines, owing to the common structural features of the two groups of drugs.
 1. Anticholinergic effects can be prominent and occur both peripherally and centrally. Amitriptyline produces the highest incidence of antimuscarinic effects. Because of these actions, caution is required in treating patients with prostatic hypertrophy and glaucoma. Tolerance often develops to these effects.
 2. Sweating is common, although its mechanism is unknown.
 3. The elderly may suffer from dizziness and muscle tremor.
 4. As with phenothiazines, cardiac arrhythmias can occur. In addition, hypotension is frequent and results from a down-regulation of adrenergic receptors.
 5. Manic excitement and delirium can occur in patients with bipolar illness.
- Acute poisoning is often treated with activated charcoal, although gastric lavage and physostigmine have been used successfully as adjuncts. Vital functions need to be supported and constantly monitored, because seizures, ventricular arrhythmias, and death can result from overdoses.
- The combination of an MAO inhibitor with a tricyclic antidepressant should be avoided, because hyperpyrexia, convulsions, and coma can result.

Selective Serotonin Hydroxytryptamine Reuptake Inhibitors (SSRIs)

Fluoxetine

Chemistry: Chemically, fluoxetine is a phenyltolylpropylamine that inhibits the uptake of serotonin.

Pharmacokinetics

- Fluoxetine is well absorbed after oral ingestion.
- It undergoes extensive hepatic biotransformation to the active metabolite norfluoxetine. The inactive metabolites are excreted in the urine.

- The elimination half-life is 1-3 days for fluoxetine and 7-15 days for norfluoxetine.

The onset of action is within 1-3 weeks after beginning of treatment.

Mechanism of action

- It is a selective inhibitor of serotonin uptake in the CNS.
- It has little effect on central norepinephrine or dopamine function.
- It has less adverse effects because of minimal binding to cholinergic, histaminic, and α -adrenergic receptors.

Therapeutic uses

- Fluoxetine is used for treatment of mild to moderate endogenous depression.
- It may be useful in treating obsessive-compulsive disorder, obesity, and alcoholism.

Adverse effects

- Fluoxetine has caused anorexia and, unlike the tricyclics, does not cause weight gain.
- It may precipitate mania or hypomania.
- Nausea, nervousness, headache, and insomnia occur more frequently with fluoxetine than with tricyclics.
- Urticaria or some other rash develops in 4% of patients.

Sertraline and paroxetine: They are similar to fluoxetine in mechanism of action and therapeutic use. Sertraline is less likely than fluoxetine or paroxetine to interact adversely with other drugs.

Bupropion

Chemistry: Chemically, bupropion is a trimethylated monocyclic phenylaminoketone.

Mechanism of action: Although the exact mechanism of action is unknown, the drug does weakly block dopamine reuptake.

Pharmacokinetics

- Bupropion is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism.
- It is eliminated primarily in the urine.

Therapeutic uses

- Bupropion is used for the treatment of major depression.
- Significant improvement is often seen within 1 week of treatment.
- Bupropion is sometimes effective in depressed patients who do not respond to tricyclics.

Adverse effects

- Bupropion does not produce sedation, orthostatic hypotension, weight gain, or the sexual dysfunction associated with other antidepressants;
- However, it is contraindicated in patients with eating disorders, seizures, or major head trauma because it may produce or exacerbate grand mal seizures.

Venlafaxine: It is chemically related to bupropion and inhibits norepinephrine and serotonin reuptake. It also weakly inhibits dopamine reuptake. High dosages may cause a sustained diastolic hypertension.

General indications (Uses) of anti-depressants

- Major (endogenous) depression.
- OCD [Obsessive-Compulsive] disorder and panic attacks.
- Generalized anxiety.
- Neuralgic pain.
- Hyperactive child or attention deficit disorder in child.
- Bed wetting (Enuresis) in child.
- Pruritus and migraine.

MOOD-ALTERING STABILIZING DRUGS

Lithium carbonate

Pharmacokinetics

- Lithium ion is well absorbed from the gastrointestinal tract and eventually reaches equilibrium between plasma and tissues.
- It is eliminated by renal excretion; 80% of the lithium is reabsorbed in the proximal tubule in the kidney.
- Lithium ion is secreted into breast milk.

Route of administration: Lithium is given orally. Because lithium has a low therapeutic index, serum concentrations must be carefully maintained between 0.8 and 1.5 mEq/L.

Mechanism of action: It is thought to be related to lithium's inhibition of hormone-sensitive adenylate cyclase and the greater stabilization of dopamine and β -adrenergic receptors.

Therapeutic indication

- The major therapeutic indications are the prevention of bipolar illness and the treatment of acute mania.
- Lithium may also be useful in reducing the intensity of depression and increasing the duration between bouts of depression in unipolar depression.

- Lithium has no effect on schizophrenia and does not produce psychotropic effects in normal individuals.

Adverse effects

- High serum concentrations of lithium are associated with anorexia, vomiting, diarrhea, excessive thirst. The latter two symptoms probably involve the ability of lithium to inhibit the action of ADH on renal adenylate cyclase. This ultimately can result in diabetes insipidus; in fact, lithium is the most common cause of nephrogenic diabetes insipidus.
- Epileptic seizures have been reported, as well as somnolence, confusion, and psychomotor disturbances.
- The use of lithium during early pregnancy can result in cardiovascular anomalies in the newborn.
- Adverse cardiovascular effects include hypotension and cardiac arrhythmias.
- Chronic lithium use can result in thyroid enlargement.
- Lithium intoxication can usually be reversed by osmotic diuresis or, in more severe cases, by dialysis.

Drugs Used in Psychiatric Disorders: Antipsychotics

Psychoactive drugs were used both for the treatment of mental illnesses (Psyche=mind) and for recreational purposes.

- In 1931 **Sen and Bose** showed that *Rauwolfia serpentina* (Sarpagandha) is useful in the treatment of insanity.
- **Electroconvulsion therapy** (ECT) was introduced in 1937 for the treatment of depression.
- In 1950 **chlorpromazine** was synthesized in France and its usefulness in psychiatric patients was demonstrated in 1952.
- During the second half of the twentieth century, extensive research has been carried out in psychopharmacology and we now have several useful drugs in this branch of pharmacology.
- Psychiatric conditions are broadly divided into neuroses and psychoses.

Neuroses (Neurotics)

- This is less serious, i.e. milder form of psychiatric disorders.
- These people build the castles in the air.
- They themselves presented to the doctors.
- Contact with reality is un-impaired in them.
- Personality of these patients are relatively undamaged.
- It includes: anxiety, mood changes, panic disorders, obsessions, irrational fears and **reactive depression** as seen following tragedies.

Psychoses (Psychotics)

- This is more severe psychiatric disorder of the two.
- These people live (stay) in the air castles, prepared by them.
- They are out of touch with reality.
- They are usually brought to the Doctors by someone else.

- There occurs a marked impairment of behavior, inability to think coherently, and to comprehend reality. Patients have no 'insight' into these abnormalities.

Psychoses could be due to:

1. **An organic cause**, i.e. there is a definable toxic, metabolic or pathological change as following head injury.
2. **Functional or idiopathic disorder**—where there is no definable cause like in schizophrenia, paranoid states and affective disorders.

The Nature of Schizophrenia

- Schizophrenia (split mind) affects about 1% of population, starts in an early age and is highly incapacitating.
- Psychotic illness characterized by delusions, hallucinations and thought disorder (positive symptoms), together with social withdrawal and flattening of emotional response (negative symptoms).
- Acute episodes (mainly positive symptoms) frequently recur and develop into chronic schizophrenia, with predominantly negative symptoms.
- Incidence is about 1% of population, with a strong, but not invariable, hereditary component.
- Pharmacological evidence is generally consistent with dopamine overactivity hypothesis, but most neurochemical evidence is negative or equivocal. Increase in dopamine receptors in limbic system (especially in left hemisphere) is consistently found.
- There is some evidence of involvement of 5-HT, and possibly other mediators, such as glutamate.

Drugs used in psychiatric illnesses may be grouped as:

- I. **Antipsychotics or neuroleptics** – used in psychoses. Specially in schizophrenia.
- II. **Antidepressants or psychotropic drugs** – used in Neuroses.
- III. **Antianxiety drugs**: used for phobic states and anxiety.
- IV. **Antimanic**: These drugs control mania, i.e. stabilizes mood.

- **Tranquilizer:** A drug which reduces stress and produces calmness, soothing with quietening effect without inducing sleep. It is an older term.
- **Neuroleptics:** They are also called as ataractic or antipsychotic or major tranquilizer.
- **Antianxiety:** Anxiolytic (sedative). They are also called as antipsychotics or minor tranquilizer.

ANTIPSYCHOTICS (NEUROLEPTICS) (Fig. 11.8.1)

Classification

1. Classical/typical neuroleptics:

- Phenothiazines:** Chlorpromazine, Triflupromazine, Thioridazine, Mesoridazine, Trifluoperazine, Fluphenazine.
- Butyrophenones:** Haloperidol, Droperidol, Trifluoperidol, Penfluridol.
- Thioxanthenes:** Thiothixene, Chlorprothixene.

2. Atypical neuroleptics: Clozapine, Olanzapine, Risperidone,

3. Miscellaneous: Reserpine, Sulpiride, Loxapine, Pimozide, Molindone, etc.

Distinction between 'typical' and 'atypical' groups is not clearly defined, but rests on:

- Incidence of extrapyramidal side-effects (less in 'atypical' group).
- Efficacy in treatment-resistant group of patients.
- Efficacy against negative symptoms (*lack of drive, social withdrawal, poverty of speech and attention impairment*).

Mechanism of action of antipsychotic drugs (Fig. 11.8.1)

- All antipsychotic drugs are antagonists at dopamine D_2 -receptors, but most also block other monoamine receptors, especially 5-HT₂. Clozapine also blocks D_4 -receptors.
- Antipsychotic potency generally runs parallel to activity on D_2 -receptors, but other activities may determine side-effect profile.
- Antipsychotic take days or weeks to work, suggesting that secondary effects (e.g. increase in number of D_2 -receptors in limbic structure) may be more important than direct effect of D_2 -receptor block.

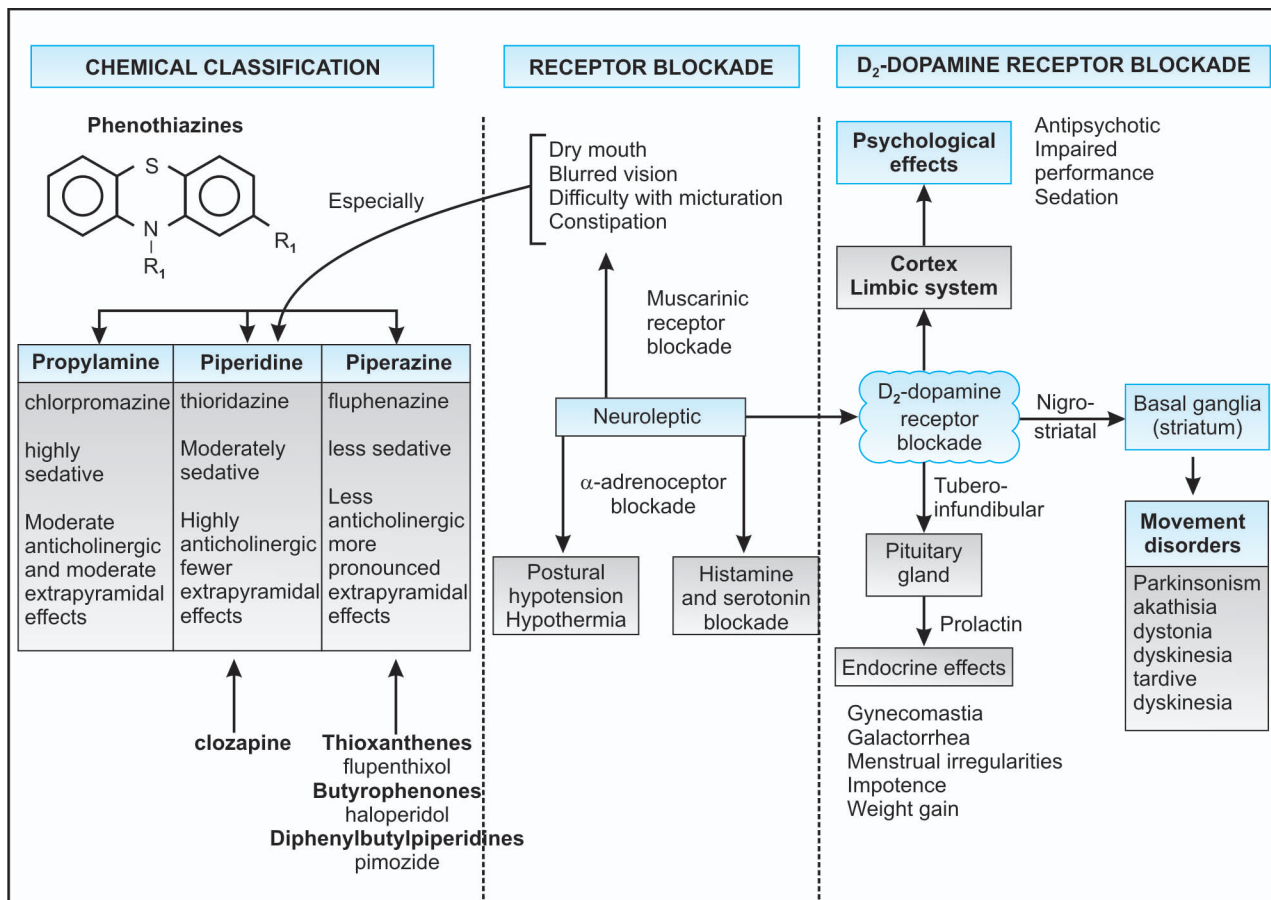


Fig. 11.8.1: Drugs used in psychosis—neuroleptics

ANTIPSYCHOTIC AGENTS (Table 11.8.1)**General considerations**

- Antipsychotic agents are prescribed for the management of psychotic symptoms; they are sometimes referred to as major tranquilizers.
- They are useful in both acute and chronic psychoses and in nonpsychotic individuals who are delusional or excited. They improve mood and behavior without producing excessive sedation.
- As a group, these agents produce little physical dependence or habituation but, notably, are capable of causing extrapyramidal symptoms, both reversible (parkinsonian symptoms, akathisia) and irreversible (tardive dyskinesia).

Phenothiazines

Chemistry: The phenothiazines have a three-ring structure in which two benzene rings are linked by a sulfur and a nitrogen atom. Differences within this group result from substitution on the nitrogen.

Pharmacokinetics

- The phenothiazines are erratically absorbed from the gastrointestinal tract.
- They are highly protein-bound and enter the fetal circulation.
- Their biologic effects last 24 for hours, allowing once-daily dosing.
- Phenothiazines are metabolized in the hepatic microsomal system by hydroxylation, followed by conjugation with glucuronic acid. In addition, the formation of sulfoxides is an important metabolic pathway.

Pharmacological effects**CNS effects:**

- The psychotic patient has fewer hallucinations and delusions. Improvements in behavior are most often noted with long-term therapy.
 - Tolerance to these effects is rarely seen.
 - The antipsychotic effects are believed to be due to antagonism of dopaminergic neurotransmission in the limbic, nigrostriatal, and hypothalamic systems.
- Extra pyramidal symptoms occur most often with chronic administration.
 - These effects arise, presumably, because of antidopaminergic effects in the basal ganglia. They can be treated by lowering the dose or by using an anticholinergic antiparkinsonian drug such as benztropine.
 - Phenothiazines having the greatest antihistaminic and anticholinergic properties will exhibit the fewest extrapyramidal effect.
- The neuroleptic effects of the antipsychotic drugs consist of emotional quieting, reduced physical movement, and a potential for neurological side effects. The drugs have little effect on the intellectual functioning of the patient.
- Most phenothiazines are antiemetic. They antagonize the agents, such as apomorphine, which stimulate the chemoreceptor trigger zone. In high doses, phenothiazines may directly depress the medullary vomiting center.
- Phenothiazines are capable of altering temperature-regulating mechanisms. *Poikilothermia*. (body temperature falls if surrounding is cold) because of failure to lose body heat.

Table 11.8.1: Common phenothiazine derivatives

Drug	Major use	Frequency of adverse effects	
		Orthostatic hypotension	Extrapyramidal symptoms
Chlorpromazine (Thorazine)	Antipsychotic	Moderate	Moderate
Clozapine (Clozaril)	Antiemetic		
Thioridazine (Mellaril)	Antipsychotic	Low	Low
Triflupromazine (Vesprin)	Anticholinergic		
Fluphenazine (Prolixin)	Antihistaminic		
Prochlorperazine (Compazine)	Antipsychotic	Moderate	Low
Promethazine (Phenergan)	Antipsychotic	Moderate	High
	Antipsychotic	Low	High
	Antiemetic	Low	Low-moderate
	Antihistaminic	Moderate	Low

- Since phenothiazines depresses the hypothalamus, endocrine alterations may occur.
 - This includes the release of lactogenic hormone prolactin, inducing lactation.
 - Abnormal pigmentation can occur because of an increased release of melanocyte-stimulating hormone from the pituitary.
 - Increased levels of prolactin may lead to galactorrhea and gynecomastia.
 - Phenothiazines decreases corticotropin release and secretion of pituitary growth hormone.

Peripheral effects

- An α -adrenergic blocking activity is seen, especially with the prototypic phenothiazine and chlorpromazine.
- Adrenergic potentiation, especially with chronic administration, is probably a result of the ability of phenothiazines to inhibit the reuptake of norepinephrine.
- Anticholinergic effects can result in blurred vision, constipation, dry mouth, decreased sweating, and rarely urinary retention. Miosis is seen with chlorpromazine and is probably due to α -adrenergic blockade. Other phenothiazines can produce mydriasis.
- Chlorpromazine is a potent local anesthetic.
- Antihistaminic activity is seen with most phenothiazine derivatives.
- Inhibition of ejaculation without interference with erection can occur, especially with thioridazine.
- Inhibition of antidiuretic hormone (ADH) secretion by chlorpromazine can result in a weak diuretic effect.
- Orthostatic hypotension can occur as a result of both the central action of phenothiazines and inhibition of norepinephrine uptake mechanisms. In addition, chlorpromazine has an antiarrhythmic effect upon the heart.
- Phenothiazines are known to enhance the pharmacological actions of barbiturates, narcotics, and ethyl alcohol.

Therapeutic indications

- Phenothiazines are used chiefly in the treatment of psychotic disorders, including **mania, paranoid states, schizophrenia**. They are given orally (chlorpromazine 100-800 mg).
 - In acute psychosis they may be given intramuscularly and responses is seen in 24 hours
 - While in chronic psychosis it takes 2-3 weeks of treatment to demonstrate the beginning of obvious response.
- In addition, several phenothiazines are effective in the treatment **of nausea and vomiting** of certain causes, such as drug-induced nausea.
- Due to their H1 antihistaminic activity, some phenothiazines are useful as **antipruritics**.

- Chlorpromazine is useful in the control **of intractable hiccup**.
- *Other neuropsychiatric syndromes* Neuroleptics are useful in the treatment of several syndromes with psychiatric, feature like psychoses associated with **chronic alcoholism and Huntington's disease**.

Adverse effects

CNS effects

- A parkinsonian syndrome may occur in which patients display rigidity and tremor at rest.
- Acute dystonic reactions may be seen with initial drug therapy. Patients display facial grimacing and torticollis.
- Tardive dyskinesia may be seen with chronic therapy. Patients display sucking and smacking of the lips and other involuntary facial movements. The dyskinesia may persist far after discontinuation of therapy.
- Lethargy and drowsiness may occur.

Cardiovascular effects

- It include orthostatic hypotension, which can result in syncope, and reflex tachycardia.

Allergic reactions: Most often occur during the first few months of therapy.

- Cholestatic jaundice can occur; it resolves with discontinuation of drug therapy.
- Blood dyscrasis (e.g., agranulocytosis) and eosinophilia can occur but are rare.
- Various forms of dermatitis may occur, including a photosensitivity reaction that resembles a severe sunburn.
 - Children exhibit extrapyramidal symptoms and, less commonly, may develop jaundice, blood dyscrasias, or hyperpyrexia.
 - Somnolence and hypotension are prominent adverse effects of acute intoxication.

Drug interactions

- Neuroleptics enhance the sedative effects of CNS depressants, alpha blockers and of anticholinergic drugs.
- When combined with these groups of drugs, the effects may be additive.
- Neuroleptics inhibit the actions of dopamine agonists and L-dopa.

Thioxanthene

- Its derivatives are chemically and pharmacologically similar to the phenothiazine derivatives.
- They differ chemically in that a carbon is substituted for a nitrogen in the central ring of the phenothiazine nucleus (position 10).
- The thioxanthenes in clinical use are chlorprothixene, thiothixene and flupenthixol.

Butyrophenones

1. The prototype is **haloperidol**, which resembles the phenothiazine derivatives pharmacologically. It has potent antiemetic properties, antagonizing stimulation of the chemoreceptor trigger zone. Significant extrapyramidal symptoms are associated with its use.
2. Another butyrophenone, droperidol, is often combined with a potent narcotic analgesic, such as fentanyl, to produce neuroleptanalgesia. This combination is known by the trade name Innovar.
3. Other included are trifluoperidol and penfluridol

Atypical Neuroleptics

Clozapine

Chemistry: It is a tetracyclic N-methyl-piperazinyl-dibenzodiazepine analog.

Pharmacokinetics

- At least 80% of orally administered clozapine (metabolites) appears in the urine or feces.
- The half-life is 12 hours.

Pharmacological effects

- Unlike standard neuroleptic and antipsychotic agents, clozapine lacks extrapyramidal side effects.
- It also differs from typical neuroleptic agents by having low affinity for D_1 and D_2 dopamine receptor.
- Clozapine has relatively potent anticholinergic activity.
- Other activities include antiadrenergic, antiserotonergic, and possible antihistaminergic activities.

Therapeutic indication

- Clozapine can be effective in treating some patients with psychosis who are unresponsive to standard neuroleptic drugs.
- It can be used safely if granulocyte counts are monitored weekly.

Adverse effects

- Although clozapine was developed 30 years ago as an antipsychotic agent, development was slowed by the recognition that it caused **agranulocytosis** in 1%-2% of patients.
- Because of the high risk of potentially fatal agranulocytosis, risk of seizures at high doses, inconvenience of weekly white cell counts, and the high cost of the drug, it is important to consider risk-benefit and cost-benefit relations (ratio)

Risperidone

Chemistry: Risperidone is a benzisoxazole derivative.

Pharmacokinetics

- Risperidone is well absorbed from the gastrointestinal tract.

- It is metabolized in the liver by the cytochrome P-450 enzymes to an active metabolite.

Mechanism of action: Risperidone has an affinity, like clozapine, for serotonin type 2 receptors and, like haloperidol, for dopamine type 2 receptors. Risperidone also binds to α -adrenergic and histamine-1 (H_1) receptors.

Therapeutic uses: Risperidone is as effective as haloperidol for chronic schizophrenia with less toxicity.

Adverse effects: It includes asthenia, sedation, and lack of concentration.

Olanzapine

- Has the advantage that it causes no EPS dysfunction and no agranulocytosis has been reported. It blocks D_2 , $5HT_2$, α_1 and α_2 , M and H_1 receptors. It has broader spectrum of activity.
- Side effect: includes constipation and dry mouth.

Sulpiride

- Selective D_2 and D_3 activity.
- Poor oral absorption.
- Less EPS than haloperidol.
- Side effect: Gynecomastia.

Clinical efficacy of antipsychotic drugs

- Antipsychotic drugs are effective in controlling symptoms of acute schizophrenia, when large doses may be needed.
- Long-term antipsychotic treatment is often effective in preventing recurrence of schizophrenic attacks, and is a major factor in allowing schizophrenic patients to lead normal lives.
- Depot preparations are often used for maintenance therapy.
- Antipsychotic drugs are not generally effective in improving negative schizophrenic symptoms.
- Approximately 40% of chronic schizophrenic patients are poorly controlled by antipsychotic drugs; clozapine may be effective in some of these 'antipsychotic-resistance' cases.

Newer ones include

- **Sertindole:** $t_{1/2}$: 3 days, effectively control negative symptoms.
- **Seroquel:** Induces tachyarrhythmias
- **Quetiapine:** Short acting ($t_{1/2}$ - 6 hrs) atypical antipsychotics.
- **Aripiprazole:** Partial agonist at D_2 receptor and $5HT_{1A}$ receptor, but antagonist at $5HT_2$ receptors.
- **Ziprasidone:** Most recently introduced atypical antipsychotic with [D_2 + $5HT_{2A}$ + H_1 + α_1] blocking activity.

Narcotic Analgesics and Antagonists

- Pain is a symptom not a disease. It is most common problem or complaint of the people in the world.

Definition: Pain or *algnesia* is an unpleasant subjective sensory and emotional experience (sensation). It cannot be easily defined. Meaning of unpleasant includes a variety of disagreeable feelings ranging from inconvenience to misery, anguish, anxiety, depression or dispersion. Pain may be associated with actual or potential tissue damage.

- Pain is a warning signal and indicates that there is impairment of structural and functional integrity of the body. It is the most important symptom that brings the patient to the doctor and demands immediate relief.
- Prompt relief of pain instills enormous confidence in the patient regarding the doctors treating ability.
- Pain arising from the skin and integumental structures, muscles, bones and joints is known as **somatic pain**. It is usually caused by inflammation and is well-defined or sharp pain
- Pain arising from the viscera is vague, dull-aching type, difficult to pinpoint to a site and is known as **visceral pain**. It may be accompanied by autonomic responses like sweating, nausea and hypotension. It may be due to spasm, ischemia or inflammation.
- When pain is referred to a cutaneous area which receives nerve supply from the same spinal segment as that of the affected viscera, it is known as **referred pain**, e.g. cardiac pain referred to the left arm.
- Pain consists of 2 components—the original ‘**sensation**’ and the ‘**reaction**’ (perception) to it. The original sensation is carried by the afferent nerve fibers and is the same in all. The reaction or perceptual component differs widely from one person to another.
- Descending pathways from the midbrain and brainstem exert a strong inhibitory effect on dorsal horn transmission. Electrical stimulation of the midbrain PAG (periaqueductal gray) causes analgesia through this mechanism.
- The descending inhibition is mediated mainly by enkephalins, 5-HT, noradrenaline and adenosine. Opioids cause analgesia partly by activating these descending pathways, partly by inhibiting transmission in the dorsal horn, and partly by inhibiting excitation of sensory nerve terminals in the periphery.
- Repetitive C-fiber activity facilitates transmission through the dorsal horn (‘wind-up’) by mechanisms involving activation of NMDA and substance P receptors.

Mechanisms of pain and nociception

Modulation of pain transmission

- Transmission in the dorsal horn is subject to various modulatory influences, constituting the ‘**gate control**’ mechanism.
- Nociception is the mechanism whereby noxious peripheral stimuli are transmitted to the central nervous system. Pain is a subjective experience, not always associated with nociception.
- Polymodal nociceptors (PMN) are the main type of peripheral sensory neuron that responds to noxious stimuli. The majority are non-myelinated C-fibers whose endings respond to thermal, mechanical and chemical stimuli.
- Chemical stimuli acting on PMN to cause pain include **bradykinin, 5-HT and capsaicin**. **PMN are sensitized by prostaglandins**, which explains the analgesic effect of aspirin-like drugs, particularly in the presence of inflammation
- Nociceptive fibers terminate in the superficial layers of the dorsal horn forming synaptic connections with transmission neurons running to the thalamus.
- PMN neurons release glutamate (fast transmitter) and various peptides (especially substance P) which act as slow transmitters. Peptides are also released peripherally and contribute to neurogenic inflammation.

- **Neuropathic pain**, associated with damage to neurons of the nociceptive pathway rather than an excessive peripheral stimulus, is frequently a component of chronic pain states, and may respond poorly to opioid analgesics.

Tachykinins

- There are three endogenous tachykinins-substance P (SP), neurokinin A (NKA) and neurokinin B (NKB), which are widely distributed in the central and peripheral nervous systems.
- Nociceptive sensory neurons express SP and NKA, and release them in the periphery and in the dorsal horn. Inflammation increase SP expression.
- SP release in the periphery when nociceptors are activated contributes to neurogenic inflammation. SP release in the dorsal horn contributes to the wind-up phenomenon.
- Nociceptive transmission and neurogenic inflammation are mediated mainly through NK_1 -receptors.
- Selective NK_1 -receptor antagonists may be developed as future analgesic compounds.

Analgesia: It is the relief of pain without loss of consciousness, as opposed to anesthesia. The chief action of opiates and similar compounds is to impair the normal sensory awareness and response to tissue injury. Analgesics only afford symptomatic relief from pain without affecting the cause.

Analgesics are of 2 classes:

- Opioid or morphine type of analgesics.
- Nonopioid or aspirin type of analgesics.

OPIOID ANALGESICS

- **Opiates** are derived from the poppy plant.
- **Opium** is the Greek name for juice. It is the dark brown gummy exudates obtained from the poppy capsule (papaver somniferous). On incising the unripe seed capsule, a milky juice emerges which turns brown on drying and this is crude opium.
- The exudate of the seed capsule contains morphine, codeine, thebaine, and papaverine. The term **opioid** refers to both naturally occurring opiates and synthetic drugs with similar actions.

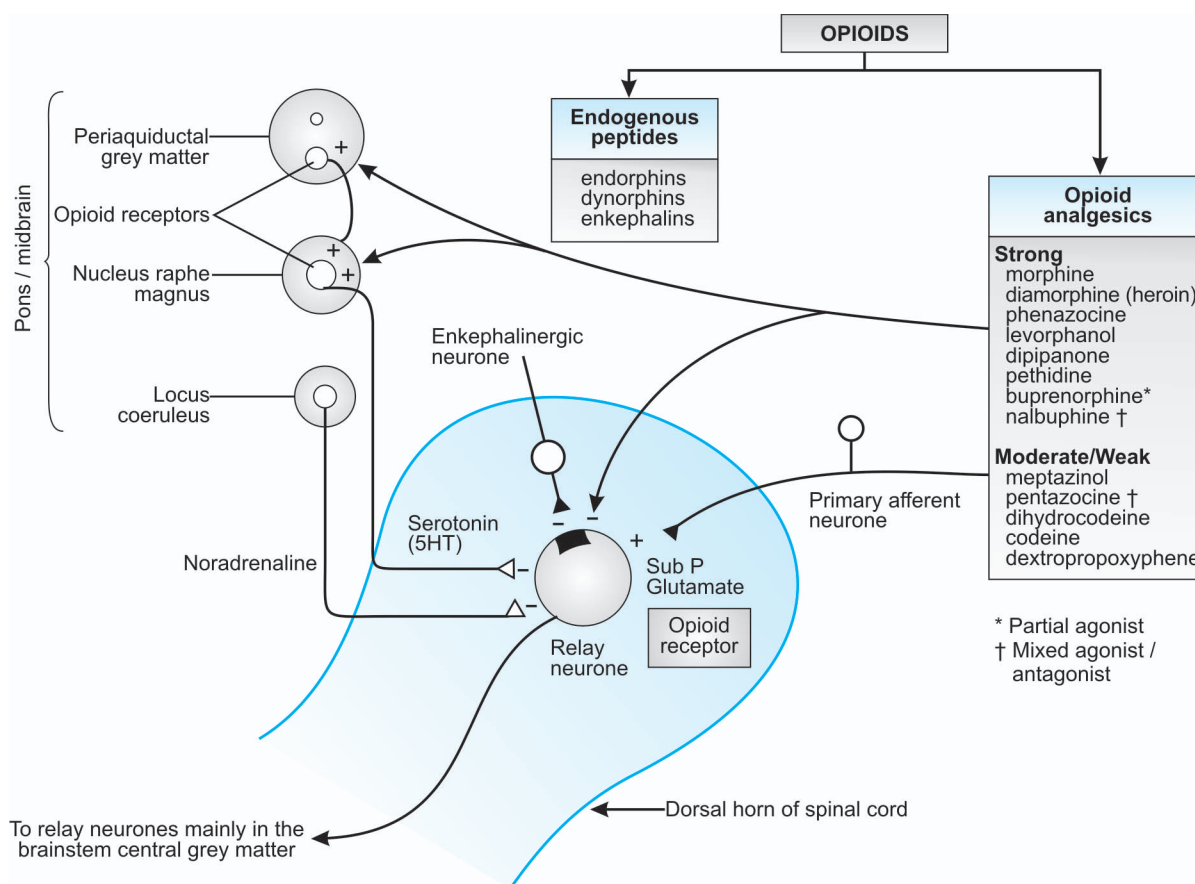


Fig. 11.9.1: Opioid analgesics

History

- Opium has been in use since 4000 BC. It was used both for medicinal and recreational purposes.
- By 18th century, opium smoking had become quite popular in Europe. It was Serturmer who isolated a pure opium alkaloid in 1806. He named it Morphine after Morpheus, the Greek God of dreams.
- As the research progressed, opium was found to contain 20 alkaloids. By around 19th century, the pure opium alkaloids were available for therapeutic use. But because they were equally abused, efforts were made to isolate the analgesic property, i.e. to obtain an *opioid* that is only analgesic and has no euphoric effects.
- In the process, various agonists, antagonists and partial agonists were synthesized. 'Opioid' is the term used for drugs with morphine-like actions. They were earlier called narcotic analgesics.

Classification

1. Agonists

Natural opium alkaloids, e.g. Morphine, Codeine, Synthetic opioids, e.g. Pethidine, Methadone

2. Antagonists: Naloxone, Naltrexone

3. Mixed agonist-antagonists: Pentazocine, Nalbuphine, Butorphanol, Buprenorphine, Nalorphine

Chemically the opium alkaloids can be grouped into:

1. The Phenanthrene group : Morphine, Codeine, Thebaine
2. The Benzyloquinoline group: Papaverine, Noscapine, Narcine.

NARCOTIC ANALGESICS (Fig. 11.9.1)

General considerations

Definitions

Analgesia is the relief of pain without loss of consciousness, as opposed to anesthesia.

Narcotic Analgesics

Morphine-like agonists

- Hydromorphone
- Oxymorphone
- Heroin

Codeine-like agonists

- Dihydrocodeine
- Hydrocodeine
- Oxymorphone

Synthetic narcotic (opioid) agonists

- Meperidine
- Fentanyl
- Methadone
- Propoxyphene
- Levorphanol

Mechanism of action

- Through the use of ligand-binding techniques, opiate receptors of several types have been identified and quantitated within the CNS. These receptors are found in the following sites.
 - The limbic system, including the amygdaloid nucleus and the hypothalamus
 - The medial and lateral thalamus and the area postrema, which is the site of the chemoreceptor trigger zone governing nausea and emesis (vomiting)
 - The nucleus of the solitary tract, which is the location of the cough center
 - The substantia gelatinosa and, to a lesser degree, other areas of the spinal cord.
- **Endogenous ligands** known as **enkephalins** are pentapeptides that are localized in some nerve endings. Their distribution closely parallels the distribution of opioid receptors. It is thought that the enkephalins may be involved in the modulation of the pain responses.
- In addition, longer polypeptides called **endorphins** possess potent analgesic activity and are found in the anterior pituitary and hypothalamus.
- Analgesia produced at opioid receptors requires binding by a molecule that has a terminal quaternary nitrogen that is capable of being charged at physiological pH and resides four or five atoms from an aromatic group.
- The interruption of pain impulses may be mediated by calcium gating via **endorphin** receptors, **enkephalin** receptors, or both.

Administration

- Patient-controlled intravenous administration of analgesics may offer advantages over intramuscular injections for some patients.
- Intraspinal opioids have been used to control postoperative and cancer pain with few adverse effects.

Opioid receptors (Fig. 11.9.2)

- **μ -receptors** are thought to be responsible for most of the analgesic effects of opioids, and for some major unwanted effects (e.g. respiratory depression, euphoria, sedation and dependence). Most of the analgesic opioids are μ -receptor agonists.
- **δ -receptors** are probably more important in the periphery, but may also contribute to analgesia.

agonist: Naltrindole (they are also responsible for reinforcing actions of opioids and reduced intestinal motility)

- **κ-receptors** contribute to analgesia at the spinal level, and may elicit sedation and dysphoria, but produce relatively few unwanted effects, and do not contribute to dependence. Some analgesics are relatively κ-selective.
- **σ-receptors** are not true opioid receptors, but are the site of action of certain psychotomimetic drugs, with which some opioids interact.
- All opioid receptors are linked through G-proteins to inhibition of adenylate cyclase. They also facilitate opening of K^+ channels (causing hyperpolarization), and inhibit opening of Ca^{2+} channels (inhibiting transmitter release). These membrane effects are not linked to the decrease in cAMP formation.

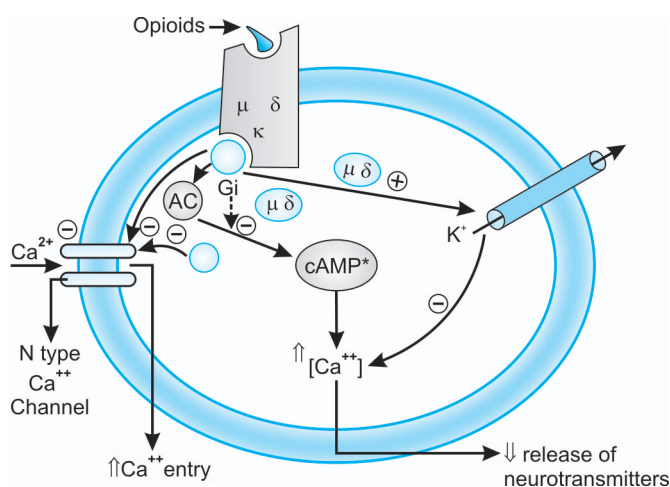


Fig. 11.9.2: Opioid receptors

Classification

Receptor type	Action
Mu (μ)	Supraspinal analgesia, respiratory depression, euphoria, physical dependence
μ_1	Analgesia
μ_2	Respiratory depression
Kappa (κ)	Spinal analgesia, miosis, sedation
Delta (δ)	Analgesia (spinal + supraspinal) Reinforcing actions Reduced intestinal motility
Sigma (σ) (non-opioid)	Dysphoria, hallucinations, respiratory and vasomotor stimulation

Morphine is the most important alkaloid of opium. Many new opioids with actions similar to morphine have been synthesized. But none of them are superior to morphine as an analgesic. Morphine is discussed as the prototype of the group.

Morphine and Related Opioids

Morphine: It is a member of the phenanthrene series of alkaloids.

Pharmacological effects

CNS effects

- Dose-related **analgesia and increased tolerance of pain** are the most prominent effects of morphine. Consciousness is not lost, and the patients can usually still locate the source of pain. Some patients become **euphoric**. If morphine is given to a person who is **pain-free, dysphoria, anxiety, or mental clouding** may be produced.
- Morphine stimulates the chemoreceptor trigger zone, **producing nausea and vomiting**. In most cases, after the first therapeutic dose, subsequent doses of morphine do not produce vomiting.
- Morphine produces **miosis** by stimulating the Edinger-Westphal nucleus, and pinpoint pupils are indicative of toxic dosage prior to asphyxia. The miosis can be blocked with atropine.
- Morphine is a powerful **respiratory depressant**, which acts by reducing the responsiveness of the respiratory centers in the brain stem to blood levels of carbon dioxide.
 1. Both alveolar and serum carbon dioxide tension (PCO_2) are increased because of the depression of medullary responsiveness.
 2. Due to the depressed respiration and increase arterial carbon dioxide retention, cerebral vasodilatation can occur, causing an increase in intracranial pressure.
 - Morphine is believed to stimulate the release of ADH (Anti-diuretic hormone), producing oliguria.
 - Morphine is a potent cough suppressant.
 - Morphine has a biphasic, dose-dependent effect on body temperature. Low doses of morphine cause a decrease in body temperature; higher doses cause an increase in temperature.

Respiration

- Morphine produces significant respiratory depression. It directly depresses the respiratory center in the brain stem. This action is dose dependent.

- It depresses all phases of respiratory activity ↓ ses rate and tidal volume. It may also alter the rhythm to produce irregular and periodic breathing.
- *Death from morphine poisoning is almost always due to respiratory arrest.*
- Morphine - suppress neurogenic (originating in RAS), chemical (hypercapnoeic) and hypoxic drive in the progressive order. The respiratory center is insensitive to increased plasma CO₂ concentration. With toxic doses breathing is maintained by hypoxic drive.
- Sedation and indifference to surroundings add to the depression.

Cardiovascular system: In therapeutic doses, morphine produces hypotension by:

- Direct peripheral vasodilatation
- Inhibition of baroreceptor reflexes
- In higher doses it causes depression of vasomotor center and histamine release contributing to a fall in BP. *Postural hypotension* (Orthostatic hypotension) and *fainting may occur* due to vasomotor medullary depression and histamine release.

GIT

- Opioids decrease the motility of the gut.
- Gastric motility is decreased resulting in increased gastric emptying time.
- Esophageal reflux may increase. Gastric acid secretion is reduced. Opioids increase the tone of the antrum and first part of the duodenum which also contribute to delayed emptying by as much as 12 hr and this can retard the absorption of orally given drugs.
- Morphine diminishes all intestinal secretions, delays digestion of food in the small intestine; resting tone is increased. There can be spasms of the intestine.
- The tone of the sphincters is increased leading to spasm. The intestinal motility (propulsive) is markedly diminished. The resulting delay in the passage of the intestinal contents in the large intestine, together with reduced secretions and inattention to the sensory stimuli for defecation relax all contribute to produce marked **constipation**.

Nausea and emesis: Morphine directly stimulates the CTZ in the medulla causing nausea and vomiting. In higher doses it depresses the vomiting center and hence there is no vomiting in poisoning. Therefore emetics should not even be tried in case of poisoning.

Pupils: Morphine produces miosis (narrowing) resulting in a characteristic pinpoint pupil in the high doses. This is due to stimulation of (EW) nucleus of the III nerve thus by a

central effect it produces miosis. *Hence morphine as eye drops does not produce miosis.*

Vagus: Morphine stimulates vagal center causing bradycardia (decrease in heart rate).

Heat regulation: Opioids shift the equilibrium point of heat-regulating center in the hypothalamus, so that body temperature falls slightly. Therefore, it produces hypothermia.

Excitatory effect: In high doses opioids produce convulsions. They may increase the excitability of the spinal cord.

Other smooth muscles

- *Biliary tract:* Morphine causes spasm of the sphincter of oddi.
- Intrabiliary pressure rises and may cause biliary colic. Atropine partly antagonises this while opioid antagonists relieve it.

Urinary bladder: Tone and amplitude of contractions of the ureter is increased : Morphine increases detrussor muscle tone in the urinary bladder, producing a feeling of urinary urgency. Vesical sphincter tone is also increased, making voiding difficult. Opioids inhibit urinary voiding reflex. All these result in urinary retention especially in elderly male with prostatic hypertrophy.

Other systemic effects

- Prolongation of labor can occur by an undefined uterine mechanism.
- Cutaneous vasodilatation secondary to histamine release can result in pruritus and sweating.

Pharmacokinetics

- If given orally ,apsorption of morphine is slow and incomplete and undergoes extensive first pass metabolism
- Bioavailability is 20 to 40 percent.
- Given subcutaneously, onset of action is in 15-20 min, peak effect–in 1 hour, duration of action is: 3-5 hour.
- Morphine is metabolized in the liver by glucuronide conjugation. The metabolites are inactive.
- 90% of the given dose is excreted in the urine, while remaining 10% is excreted in the feces. This latter component is derived from bile as conjugated morphine which participate in entero-hepatic circulation.

Adverse effects

- Respiratory depression is the most important effect and is dose-dependent.
- Nausea and sometimes dysphoria can occur.
- Increased biliary tract pressure can occur, and caution should be exercised in giving opiates to patients with gallbladder disease.

- Long-term chronic administration can result in **physical dependence**. Pinpoint pupils are a consistent finding in addiction.
- **Allergic reactions can occur**, and skin rashes are a common manifestation.
- Due to morphine's bronchoconstrictive action, the drug is contraindicated for asthmatic patients.
- Some phenothiazines are capable of producing antianalgesia when combined with an opiate such as morphine, whereas other phenothiazines can enhance the analgesic action of morphine. However, phenothiazines are likely to increase the sedative and respiratory depressant effects of opioids.

Tolerance and Dependence

Tolerance: Tolerance develops rapidly, accompanied by physical withdrawal syndrome.

- The mechanism of tolerance may involve adaptive up-regulation of adenylate cyclase. It is not pharmacokinetic in origin and receptor down-regulation is also not a major factor
 - Repeated administration of morphine results in the development of tolerance to some of its effects, i.e. respiratory depression, analgesia, sedation and euphoriant effects and other CNS depressant effects.
 - Constipation and miosis show no tolerance. Though lethal dose of morphine is about 250 mg, addicts can tolerate morphine in grams.
 - Patients with pain can also tolerate a higher dose of morphine.
 - Cross-tolerance is seen among different opioids. An addict needs progressively higher doses to get his 'kick' or 'rush'.
- Physical addiction occurs, although the morphine withdrawal syndrome is not as severe as barbiturate withdrawal.

Dependence

- Dependence is satisfied by μ -receptor antagonists.
- Dependence comprises two components: (a) physical dependence, associated with the withdrawal syndrome, lasting for a few days; (b) psychological dependence associated with craving, lasting for months or years. Psychological dependence rarely occurs in patients being given opioids as analgesics.
- Opium has been a drug of addiction for many centuries. Its ability to produce euphoria makes it a drug of addiction.
- Opioids produce both psychological and physical dependence. Sudden cessation of opioids or administration of opioid antagonists produces significant withdrawal symptoms in such dependent individuals.

- Manifestations are lacrimation, sweating, yawning, anxiety, apprehension, restlessness, rhinorrhea and tremors – seen 8-12 hr after the last dose. The person craves for the drug. As the syndrome progresses; fever, insomnia, abdominal colic, severe sneezing, violent yawning, diarrhea, blurring of vision due to mydriasis, hypertension, severe dehydration, gooseflesh, palpitation, prostration and cardiovascular collapse can occur. **Abdominal cramps, pain in the bones and muscles of the back and limbs are also characteristic.**

Management of addiction: Morphine is slowly withdrawn over several days and substituted by **oral methadone**. Advantage of methadone administration is:

- **Methadone** is effective orally and by this route no 'kick' is experienced.
- It is more potent, long-acting (μ -receptor agonists) and prevents withdrawal symptoms.
- The dose is adjusted as per the degree of dependence: **1 mg methadone** for every 4 mg of morphine (once a day). Methadone is then gradually withdrawn.
- Most addicts can be completely withdrawn from opioids in about 10 days though mild tolerable withdrawal symptoms persist.
- **Clonidine** a central α_2 agonist can suppress some of the autonomic withdrawal symptoms like anxiety, nausea, vomiting and diarrhea. It is given for 7-10 days and withdrawn over 3-4 days.
- Night time sedation with a **hypnotic** is helpful.

Therapeutic indications of morphine

- **Analgesic:** Morphine is one of the most potent analgesics available. It affords symptomatic relief of pain without affecting the underlying disease. It is an excellent analgesic for severely painful conditions such as acute myocardial infarction, fractures, burns, pulmonary embolism, terminal stages of cancer, acute pericarditis, spontaneous pneumothorax and postoperative pain. In excruciating pain, **morphine can be given IV**.
- **As preanesthetic medication:** They (morphine or Pethidine) reduces anxiety, provide analgesia, allow smoother induction and reduce the dose of the anesthetic required.
- **Acute left ventricular failure:** Morphine is used to alleviate the dyspnea of LVF and pulmonary edema in which the response to IV morphine may be dramatic. The mechanism is not clear.
- **Diarrhea:** Opioids are effective for the symptomatic treatment of diarrhea. Synthetic opioids—diphenoxylate and loperamide are preferred as antidiarrheals.

- **Cough:** Though morphine is an effective antitussive, codeine is the preferred opioid for this purpose. But now many nonaddictive antitussives are available.
- **Sedative:** Morphine relieves anxiety in threatened abortion without affecting uterine motility. It is an useful sedative in the presence of pain.
- **Special anesthesia**
 - High doses of morphine can be used IV to produce general anesthesia.
 - Neuroleptanalgesia - fentanyl can be used to produce neuroleptanalgesia with droperidol.
 - Morphine can be used epidurally for the relief of post-operative and chronic pain.
 - Dose: Morphine 10 to 20 mg IM/SC; 20 mg tab is now available (ethyl morphine) for oral use.

Acute morphine poisoning

- It may be accidental, suicidal or homicidal.
- Lethal dose in non-addicts is about 250 mg but addicts can tolerate grams of morphine.
- *Signs and symptoms.* include respiratory depression with shallow breathing, pin point pupils, hypotension, shock, cyanosis, flaccidity, stupor, hypothermia, coma and death due to respiratory failure and pulmonary edema.

Treatment

- Positive pressure ventilation.
- Maintenance of BP.
- Gastric lavage with potassium permanganate to remove unabsorbed drug
- Specific antidote is naloxone 0.4-0.8 mg IV repeated every 10-15 min.

Precautions and Contraindications

- Avoid opioids in patients with respiratory insufficiency: i.e. COPD.
- An attack of bronchial asthma can be precipitated by morphine.
- In extremes of age – more susceptible to respiratory depression.
- **Head injury** – morphine is contraindicated because:
 1. Morphine increases CSF pressure by retaining CO_2 and thereby increases the intracranial tension.
 2. Causes marked respiratory depression.
 3. Vomiting, miosis and mental clouding seen with morphine interfere with diagnosis and assessment of progress in head injuries.
- In hypovolemic shock, morphine further decreases the BP.
- Undiagnosed acute abdomen – morphine relieves pain and may interfere with the diagnosis.

Codeine

Chemistry: Codeine is the 3-methyl ether of morphine. It can be obtained from opium or synthesized by methylation of morphine.

- Although the pharmacological effects of codeine are similar to those of morphine, it has about one-twelfth the analgesic potency of morphine, and it is generally used for somewhat milder pain.
- Codeine has a high oral-parenteral potency ratio so that when it is administered orally, it is 60% as potent as when injected intramuscularly.
- An oral dose of 30 mg of codeine is equivalent in analgesia to 600 mg of aspirin.
- Codeine is also very useful as a cough suppressant.
- Codeine produces less sedation or respiratory depression than morphine and fewer gastrointestinal effects.
- Addiction liability is lower than with morphine, and withdrawal is less severe.

Hydrocodone and oxycodone or Hydrocodeine and Oxycodeine

- Although these agents are codeine derivatives, they possess an analgesic potency closer to that of morphine.
- Their potential for causing respiratory depression is also greater than that of codeine; this is especially true of oxycodone.
- They possess a significant addiction liability.

Heroin

- Heroin is diacetylated morphine.
- Heroin has a more rapid onset and shorter duration of action than morphine.
- It has an analgesic potency greater than that of morphine : 3 mg of heroin is equivalent to 10 mg of morphine.
- Heroin is not used clinically in the United States.

Hydromorphone

- Hydromorphone is 10 times more potent than morphine in producing analgesia with correspondingly more respiratory depressant activity.
- Hydromorphone is less nauseating and less constipating than morphine.
- It has highly physically addicting liability.
- Hydromorphone can be administered orally, parenterally, or rectally.

Levorphanol: It produces effects similar to those of morphine but with a lower incidence of nausea and vomiting.

MEPERIDINE AND CONGENERS

Meperidine (Pethidine): It is a phenylpiperidine derivative, an entirely synthetic analgesic.

- It is about one-eighth as potent as morphine, 100 mg of meperidine being equivalent to 15 mg of morphine.
- Meperidine is well absorbed by all routes of administration and is better absorbed orally than is morphine. Excretion is mainly in the urine.
- Meperidine causes respiratory depression and possesses addiction liability, although withdrawal effects are less severe than with morphine.
- Meperidine causes histamine release and smooth muscle spasm, including bronchospasm.
- It possesses weak, atropine-like activity and tends to cause mydriasis. In toxic doses, the pharmacological effects are, in part, atropine-like.
- With intravenous administration, the incidence of adverse effects is increased. Repeated intramuscular administration can produce tissue irritation.
- Meperidine has no gastrointestinal or antitussive action.

Diphenoxylate: It is a derivative of meperidine (Pethidine), available in combination with atropine (e.g. Lomotil).

- Its principal use is to control diarrhea.
- In the recommended dosage, it causes few morphine-like subjective effects and has low addiction liability.
- Due to the atropine in the combination, adverse effects, such as dry mouth and blurred vision, prevent abuse.

Fentanyl, like diphenoxylate. It is a congener of meperidine (Pethidine).

- It has 80 times the analgesic potency and respiratory depressant properties of morphine, and is more effective than morphine in maintaining hemodynamic stability.
- When combined with droperidol, it produces dissociative analgesia or neuroleptanalgesia.
- Its principal use is in anesthesia, where it is administered parenterally. It has a rapid onset and short duration of action. Fentanyl is also available in a controlled-release transdermal formulation. Therapeutic concentrations are not reached for 8-12 hours after application of the first dose. It is useful for the treatment of chronic cancer pain.
- High doses of fentanyl are capable of producing muscular rigidity.

Sufentanil: It is used as a short-acting anesthetic adjunct; it has a shorter onset of action than fentanyl.

Alfentanil. It is a synthetic opioid analgesic related to fentanyl and sufentanil.

- It has a more rapid onset of action and shorter duration of narcotic effect than fentanyl.
- It is used as an adjunct to general anesthetics and as an anesthetic induction agent.

METHADONE AND CONGENERS

Methadone is a modified diphenylheptane

- This synthetic analgesic has pharmacological properties similar to those of morphine, but it is more effective orally than morphine.
- The duration of analgesia with methadone is equal to that of morphine, although the half-life of methadone is longer. This can result in cumulative toxicity.
- Methadone is well absorbed from the gastrointestinal tract, undergoes extensive biotransformation in the liver, and is excreted in both the urine and bile.
- Its principal uses are in analgesia, in the suppression of withdrawal symptoms due to opiate addiction, and in treatment of heroin users.
 - In methadone maintenance, opiate addicts receive periodic oral doses of methadone.
 - In appropriate doses, methadone satisfies the craving for heroin without producing euphoria or somnolence.
 - Because of cross-tolerance, the effects of other self-administered opiates are blocked.
- Adverse effects are similar to those caused by morphine.
- Both tolerance and physical dependence can occur with methadone administration. Methadone withdrawal is less severe than the withdrawal from other opiates.

Propoxyphene/Dextro-propoxyphene: It is a structural analog of methadone with a spectrum of pharmacological activity similar to that of codeine.

- Propoxyphene is not an anti-inflammatory agent; therefore, it is less effective in treating pain associated with inflammation. In analgesic potency, it closely resembles codeine. When combined with aspirin, propoxyphene produces more analgesia than either drug alone; however, the combination of aspirin and codeine is less costly than that of aspirin and propoxyphene.
- The water-soluble hydrochloride is absorbed more rapidly.
- The N-demethylated metabolites are slowly excreted in the urine.
- Propoxyphene depresses respiration about one-third as much as codeine.
- The incidence of abuse is comparable to that seen with codeine.
- Physical dependence and tolerance can occur but usually are seen only after chronic high-dose administration.

OPIOID RECEPTOR ANTAGONISTS AND PARTIAL ANTAGONISTS

Partial agonists and mixed agonists/antagonists

- Buprenorphine (partial agonist)
- Nalorphine (partial agonist)
- Pentazocine (mixed agonist/antagonist)
- Butorphanol (mixed agonist/antagonist)
- Nalbuphine (mixed agonist/antagonist)

Full antagonists

- Naloxone
- Naltrexone

Buprenorphine: It is a **partial antagonist** with low potential for abuse (it is a schedule V drug).

- Its onset of action is within 15 minutes when given parenterally.
- It is metabolized in the liver and excreted in the feces and urine.
- The respiratory depression caused by buprenorphine is quantitatively similar to that caused by morphine.
- Buprenorphine can precipitate withdrawal symptoms in narcotic-addicted patients.
- Buprenorphine's pharmacologic activity is not easily reversed, even with high doses of naloxone.

Nalorphine: It was originally used as an opioid antagonist.

- When it became recognized that it possessed analgesic properties with less respiratory depression than morphine and nalorphine, it became classified as a partial antagonist.
- Nalorphine can produce withdrawal symptoms when it is given to narcotic-dependent patients.

Pentazocine: It is a benzomorphan derivative with moderate agonistic and weak antagonistic activity.

- Due to its antagonistic activity, pentazocine can precipitate withdrawal in addicts.
- Although pentazocine is similar to morphine in pharmacological properties, it has one third the analgesic potency. A dose of 30 mg, given parenterally, produces analgesia equivalent to 10 mg of morphine; if given orally, 50 mg is equivalent to 60 mg of codeine.
- Pentazocine is well absorbed from the gastrointestinal tract as well as from subcutaneous and intramuscular sites. Pentazocine is biotransformed in the liver and excreted via the kidney.
- **Adverse effects**
 - Pentazocine can produce psychotomimetic effects, such as anxiety and hallucinations.

- There may be nausea, but less so than that associated with other opioids.
- Analgesic doses are capable of increasing the pulmonary artery pressure and cardiac work ($\uparrow$ HR + $\uparrow$ BP).
- Respiratory depression with higher doses is less pronounced than with comparable doses of morphine.
- Tolerance to the analgesia can develop.
- Pentazocine possesses both physical dependence potential and psychological dependence potential.

Butorphanol: It has actions similar to those of pentazocine.

- As the analgesic dose is increased, respiratory depression is not increased proportionately.
- Pulmonary artery pressure and myocardial work are increased at analgesic doses.
- Unlike pentazocine, butorphanol does not precipitate a withdrawal syndrome in opioid addicts.

Nalbuphine: Although structurally it is similar to naloxone, it is equivalent (on a weight basis) to morphine in producing analgesia.

- It is considered to be a partial antagonist. Although its antagonistic properties are weak, it precipitates withdrawal in the opioid addict.
- Nalbuphine produces respiratory depression, but doses beyond 30 mg produce no further depression.
- Unlike pentazocine and butorphanol, nalbuphine does not cause adverse cardiac effects.
- Nalbuphine possesses abuse potential, and physical dependence has been reported.

Naloxone: It is an N-allyl derivative of oxymorphone, is a full antagonist.

- Naloxone, like other competitive receptor antagonists, blocks the opioid receptor.
- The sedative effects, respiratory depression, and adverse cardiovascular effects of opioid agonists are reversed within 1-2 minutes after parenteral administration of naloxone. There may be an "overshoot," producing increased respiration for a short period of time.
- The duration of the antagonistic effect is dose-dependent and usually lasts 1-4 hours.
- If naloxone is administered to opioid-addicted patients, a withdrawal syndrome is easily precipitated.
- Tolerance to the antagonistic effects does not develop.
- Naloxone is usually administered parenterally. It is metabolized in the liver via glucuronide conjugation.
- In obstetrics, mothers who have received opioids during labor may be given a dose of naloxone just prior to delivery to minimize neonatal respiratory depression. Alternatively, naloxone can be administered to the neonate via the umbilical vein.

Naltrexone

- Naltrexone, another full antagonist, is now the treatment of choice for patients addicted to heroin or other opioids.
- It can be administered orally.
- It has twice the potency of naloxone and three times the duration of action.
- An opioid abstinence syndrome can result if naltrexone is administered too vigorously.
- Naltrexone may cause insomnia, anxiety, abdominal cramping, nausea, and joint pain.
- It is contraindicated in patients with acute hepatitis or hepatic failure.
- Alcohol craving is also reduced.

Nonopioid Antitussives (Dextromethorphan)

- Dextromethorphan is the *disomer* of the codeine analog of levorphanol.
- In contrast to the *isomer*, dextromethorphan does not possess analgesic or Addictive properties, and its principal use is as a cough suppressant.
- It is as effective as codeine in cough suppression, It does not suppresses CNS, although at high doses, CNS depression may occur.
- It is commonly found in over-the-counter formulations.
- It does not suppresses mucociliary function and also devoid of constipation.

Central Nervous System Stimulants and Psychotomimetics

CNS stimulants drugs may be broadly divided into:

- 1. Respiratory stimulants/Analeptics:** Doxapram, Amiphenazole, Nikethamide
- 2. Convulsants:** Leptazol, Strychnine, Picrotoxin, Bicuculline, etc.
[They have no clinical use: Experimental tools only]
- 3. Psychomotor stimulants:** These drugs increase motor activity, produce excitement and euphoria.

Amphetamine

- Dexamphetamine
- Methylphenidate
- Fenfluramine

Cocaine, Methylxanthines and MDMA (Methylene dioxy methamphetamine)

- 4. Psychotomimetics drugs (Hallucinogens):** These drugs affect thought, perception mood and behavior.

They are also termed as Psycho-dysleptics, Psychogenic, Psychodelic, Psychotoxics, and fantastics. E.g. Cocaine, LSD (Lysergic acid diethylamide), Cannabis, etc. (See Fig. 11.10.1).

Convulsants and Respiratory Stimulants

- This is a diverse group of drugs which have little clinical use.
- **Respiratory stimulants are also called Analeptics.**
- Certain short-acting respiratory stimulants (e.g. doxapram, amiphenazole, and nikethamide) can be used in respiratory failure. Though they may bring about temporary improvement in respiration, the mortality is not reduced. They have a low safety margin and may produce convulsions.

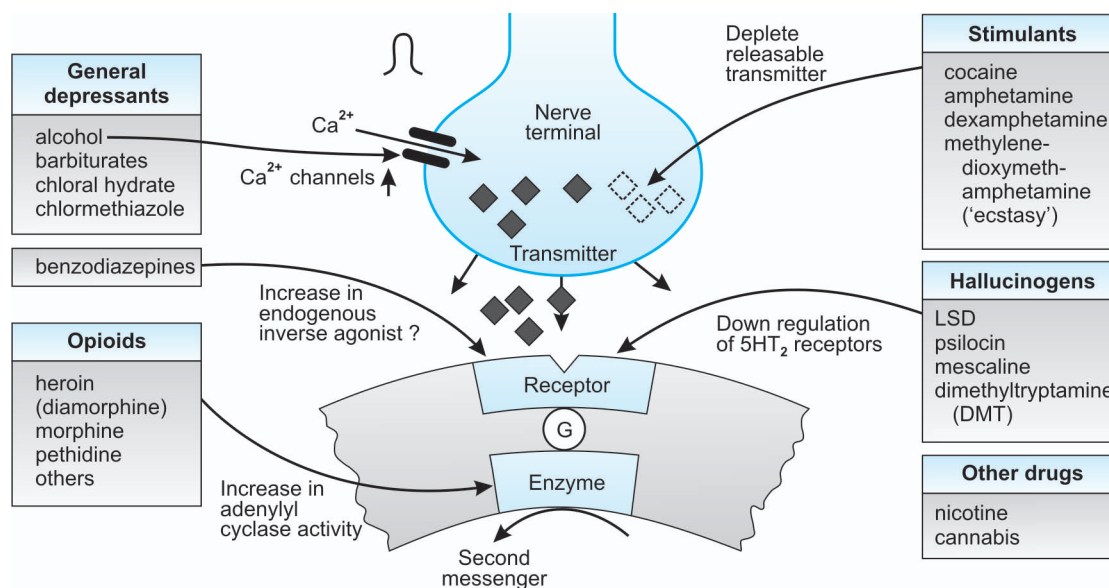


Fig. 11.10.1: Mechanism of action of central nervous system stimulants, depressants, hallucinogens and opioids

Doxapram and Amiphenazole: Appears to act mainly on the brainstem and spinal cord and increases the activity of respiratory and vasomotor centers.

Adverse effects: Nausea, cough, restlessness, hypertension, tachycardia, arrhythmias and convulsions.

Uses

- Doxapram is occasionally used IV as an analeptic in acute respiratory failure
- Apnoea in premature infants not responding to theophylline.

Nikethamide is not used because of the risk of convulsions.

Strychnine is a convulsant poison that acts mainly on the spinal cord, by blocking receptors for the inhibitory transmitter, glycine. It also resembles tetanus (caused by clostridium tetani); blocks glycine release. Also resembles botulinum toxin (clostridium botulinum). In small doses increases auditory and visual acuity therefore rarely used as **tonics** (for brain and body)

Picrotoxin and bicuculline act as GABA_A-antagonists; bicuculline blocks GABA_A-receptor site (it is a good experimental tool for GABA_A-R transmission, whereas picrotoxin appears to block the ion channel (Cl⁻) produces convulsions.

Leptazol works by an unknown mechanism. Leptazol induced convulsions provide an animal model for testing anticonvulsant drugs, giving good correlation with effectiveness in preventing absence seizures.

Psychomotor Stimulants

- Amphetamine and dextroamphetamine are sympathomimetic drugs.
- Cocaine is a CNS stimulant, produces euphoria and is a drug of abuse.

Amphetamines

- The main effects are:
 - increased motor activity
 - euphoria and excitement
 - anorexia
 - with prolonged administration, stereotyped and psychotic behavior.
- Effects are mainly due to release of catecholamines, especially noradrenaline and dopamine.
- Stimulant effect lasts for a few hours, and is followed by depression and anxiety.
- Tolerance to the stimulant effect develops rapidly, though peripheral sympathomimetic effects may persist.

- Amphetamines may be useful in treating narcolepsy, and also (paradoxically) to control hyper kinetic children. **Dexfenfluramine** is used as an appetite-suppressant.
- Their main importance is in drug abuse.

Cocaine

- Cocaine acts by inhibiting catecholamine uptake (especially dopamine) by nerve terminals.
- Behavioral effects of cocaine are very similar to those of amphetamines, though psychotomimetic effects are rare. Duration of action is shorter.
- Cocaine used in pregnancy impairs foetal development, and may produce foetal malformations.
- As drugs of abuse, amphetamines and cocaine produce strong psychological dependence, and carry a high risk of severe adverse reactions.

Methyl-xanthines

- Caffeine and theophylline produce psychomotor stimulant effects. Caffeine, theophylline and theobromine are the naturally occurring xanthenes alkaloids.
- The beverages – coffee contains caffeine; tea contains theophylline and caffeine; cocoa has caffeine and theobromine.
- Average caffeine consumption from beverages is about 200 mg/day.
- Main psychological effect is reduced fatigue and improved mental performance (alertness), without euphoria a reduction of fatigue, produce a sense of well-being and improve motor activity and performance with a clearer flow of thought. Even large doses do not cause stereotyped behavior or psychotomimetic effects.
- Methyl-xanthines act mainly by antagonism at A₂ purine receptors, and partly by inhibiting phosphodiesterase, thus producing effects similar to those of β-adrenoceptor agonists.
- Peripheral actions are exerted mainly on heart, smooth muscle and kidney.
- Theophylline is used clinically as a bronchodilator; caffeine is not used clinically.

CVS

- Methyl-xanthines increases the force of contraction of the myocardium and increase the heart rate and therefore increase the cardiac output.
- They also produce peripheral vasodilatation which tends to decrease the BP.
- The changes in BP are therefore not consistent. Caffeine causes vasoconstriction of cerebral blood vessels.

Kidneys: Xanthines have a diuretic effect and thereby increase the urine output.

Smooth muscle: Xanthines cause relaxation of smooth muscles especially the bronchial smooth muscle.

Skeletal muscle: Xanthines enhance the power of muscle contraction and thereby increase the capacity to do muscular work by both a central stimulant effect and the peripheral actions.

GI tract: Xanthines increase the secretion of acid and pepsin in the stomach and are gastric irritants.

Adverse effects

- It includes *nervousness, insomnia, tremors, tachycardia, hypotension, arrhythmias, headache, gastritis, nausea, vomiting, epigastric pain and diuresis*.
- High doses produce **convulsions**.
- Tolerance develops after sometime. Habituation to caffeine is common.

Uses

- **Headache:** *Because of the effects of caffeine on cerebral blood vessels, it is combined with ergotamine for the relief of migraine headache. Caffeine is also combined with aspirin/paracetamol for the treatment of headache.*
- **Bronchial asthma:** Theophylline is used in the treatment of bronchial asthma.

Psychotomimetic Drugs

- The main types are:
 - LSD, psilocybin and mescaline (actions related to 5-HT and catecholamines)
 - Phencyclidine.
- The main effect is to cause sensory changes, hallucinations and delusions, resembling symptoms of acute schizophrenia.
- They are not used clinically, but are important as **drugs of abuse**.
- LSD is exceptionally potent, producing a long-lasting sense of dissociation and disordered thought, sometimes with frightening hallucinations which can lead to violence. Hallucinatory episodes can recur after a long interval.

- LSD and phencyclidine precipitate schizophrenic attacks in susceptible patients, and LSD may cause long-lasting psychopathological changes.
- LSD appears to act as an agonist at 5-HT receptors, and suppresses electrical activity in 5-HT neurons, and action which appears to correlate with psychotomimetic activity.
- They do not cause physical dependence, and tend to be aversive, rather than reinforcing, in animal models.
- The mechanism of action of phencyclidine is complex, it binds to the σ -receptor, (activate them) and also blocks the glutamate activated NMDA-receptor channel, as well as interacting with other neurotransmitter systems.

Cannabinoids: Most popular recreational and ritualistic intoxicant used for millennia.

- Bhang → dried leaves
 - Ganja → Female inflorescence.
 - Charas → resinous extract.
- } act through CB₁ (brain), CB₂ (periphery) receptors

Drug dependence: *Dependence is defined as an excessive craving which develops as a result of repeated administration of the drugs.*

- Dependence occurs with a wide range of psychotropic drugs, acting by many different mechanisms.
- The common feature of dependence-producing drugs is that they have a positive reinforcing action ('reward') associated with activation of the meso-limbic dopaminergic pathway.
- Dependence is often associated with
 - a. tolerance** to the drug, which can arise by various biochemical mechanisms;
 - a physical abstinence syndrome**, which varies in type and intensity for different classes of drug;
 - c. psychological dependence (craving)**, which may be associated with the tolerance-producing biochemical changes.
- Psychological dependence, which usually outlasts the physical withdrawal syndrome, is the major factor leading to relapse among treated addicts.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are aspirin-type or nonopioid analgesics.

- They have anti-inflammatory, antipyretic and uricosuric properties – without addiction liability.
- The medicinal effects of the bark of the willow tree has been known since centuries. The active principal 'salicin' was isolated from the willow bark. This salicin is converted to glucose and salicylic acid in the body.
- In 1875, sodium salicylate was first used in the treatment of rheumatic fever. After its anti-inflammatory and uricosuric properties were established, efforts were made to synthesize derivatives which were less expensive.
- Now they have replaced the natural ones in the market.

Classification (Fig. 11.11.1)

1. *Salicylic acid derivatives* – Aspirin, Sodium salicylate, Diflunisal
2. *Para-aminophenol derivatives* – Paracetamol, Phenacetin.
3. *Pyrazolone derivatives* – Phenylbutazone, Azapropazone, Metamizol, Propiphenazone
4. *Indole acetic acid derivatives* – Indomethacin, Sulindac
5. *Arylacetic acid derivatives* – Diclofenac, Ketorolac, Tolmetin
6. *Propionic acid derivatives* – Ibuprofen, Fenoprofen, Carprofen, Naproxen, Ketoprofen
7. *Anthranilic acids (Fenamates)* – Flufenamic acid, Mefenamic acid, Enfenamic acid
8. *Oxicams* – Piroxicam, Tenoxicam
9. *Alkanones* – Nabumetone
10. *Sulfonanilide derivative* – Nimesulide, Celecoxib.

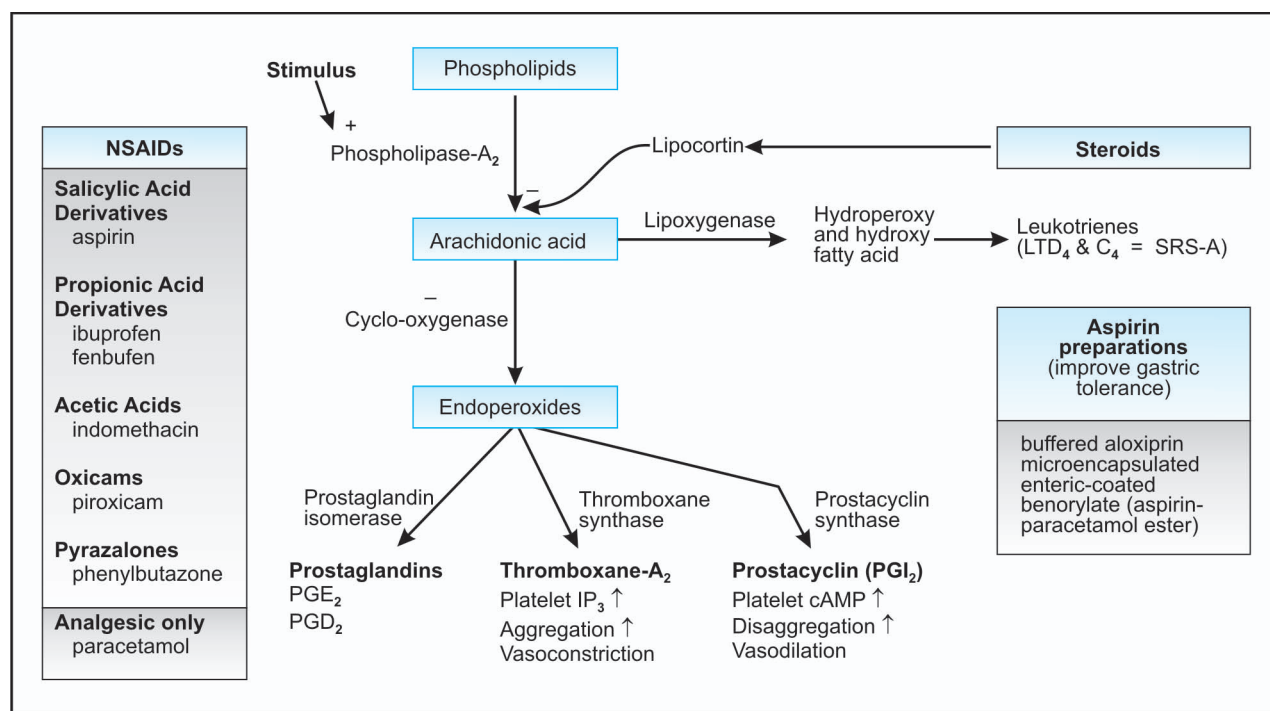


Fig. 11.11.1: Nonsteroidal anti-inflammatory drugs (NSAIDs)

SALICYLATES: Salicylates are salts of salicylic acid, e.g. methyl salicylate, sodium salicylate, acetyl salicylic acid (aspirin). Aspirin is taken as the prototype.

Aspirin

Chemistry: Aspirin was first isolated in 1829 by Leroux from willow bark, yielding a bitter glycoside called **salicin**, a white crystalline substance. It is stable in dry air but hydrolyzes to salicylic and acetic acids in moist air.

Pharmacokinetics

Absorption

- Oral absorption of salicylates is fairly rapid, with appreciable blood levels appearing within 30 minutes and peaking at about 2 hours.
 - Upon oral administration of the salicylates, a portion is rapidly absorbed from the stomach.
 - However most of an orally ingested salicylate is absorbed from the upper portion of the small intestine.
- Rectal absorption of the salicylates is slow and unpredictable.
- Salicylic acid and methyl-salicylates are absorbed from the intact skin.

Distribution

- Once absorbed, the salicylates are distributed throughout the body by a pH-dependent passive diffusion process.
- Most of the salicylates bind avidly to serum proteins. Aspirin binds to a lesser extent.

Biotransformation

- Aspirin is deacetylated in the liver, plasma and other tissues to release salicylic acid which is the active form
- Biotransformation of salicylates occurs in the microsomal drug-metabolizing system, and the following metabolic products are seen in the urine: **salicyluric acid** (75%), **phenolic glucuronide** (10%), **acyl glucuronide** (5%), and free **salicylic acid** (10%).

Excretion

- Plasma $t_{1/2}$ of aspirin is 3-5 hours.
- Elimination is dose dependant. It follows first order kinetics in small doses and zero order kinetics in higher doses. Therefore at anti-inflammatory doses, $t_{1/2}$: increases to 12 hours. Salicylates are excreted in urine.
- Alkalinization of urine (pH : 8) significantly increases the excretion of salicylates because of increased ionization and decreased reabsorption through the renal tubules.

Mechanism of Action (Fig. 11.11.1)

For either salicylates (e.g. aspirin) or nonsalicylates (e.g. ibuprofen)

- Aspirin and most NSAIDs exert their anti-inflammatory and analgesic action via inhibition of prostaglandin (PGs) biosynthesis.
 - By inhibiting the cyclooxygenase (COX) enzyme, these agents inhibit the formation of PGE_2 , PGI_2 and PGF_2 , which are powerful mediators of vasodilation, pain, and edema associated with inflammation.
 - There are two types of cyclo-oxygenase: COX-1 and COX-2. COX-1 is constitutive in nature meaning that it is always present at various sites like blood vessels, stomach and kidney. COX-2 sets in whenever there is inflammation.
 - The traditional NSAIDs are non-selective, inhibiting both the enzymes. Newer NSAIDs are developed to selectively inhibit COX – 2, so that they are free from adverse effect on GIT ulcers.
 - Thromboxane A_2 (TXA_2) formation is also inhibited, which is clinically evidenced by prolonged bleeding times. This reduced thrombus formation becomes clinically significant in the postmyocardial infarction patient; an aspirin regimen has been demonstrated to increase long-term survival.

Pharmacological effects (Actions)

1. Analgesic effects

- The analgesia is usually effective for low-to moderate-intensity pain; integumental pain is relieved better than pain from hollow visceral areas.
- Relief of pain occurs through both peripheral and central mechanisms.
 - Peripherally, the salicylates inhibit the synthesis of PGs in inflamed tissues, thus preventing the sensitization of pain receptors to both mechanical and chemical stimuli.
 - Centrally, the analgesic site exists in close proximity to the antipyretic region in the hypothalamus. The analgesia produced by the salicylates is not associated with mental alterations, such as hypnosis or changes in sensation other than pain.

2. Antipyretic action

- Aspirin is rapidly effective in febrile patients, yet has little effect on normal body temperature, suggesting that PGs have little influence on normal homeostatic mechanisms for body temperature.
- The antipyretic action is centrally mediated; the central nervous system (CNS) action is thought to be due to inhibited PGE_2 synthesis from the hypothalamus in response to an endogenous pyrogen.

- Hyper-pyrexia can occur in salicylate toxicity, but this is partially the result of an increase in oxygen consumption and metabolic rate.

3. Anti-inflammatory effects

- Salicylates, and NSAIDs in general, are anti-inflammatory due to the inhibition of PG synthesis; however, there is a wide range of potency.
- The primary clinical application is in the treatment of musculoskeletal disorders, such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.
- Although these agents may provide symptomatic relief from pain or joint stiffness. Occult joint damage may still occur to the point of necessitating an additional regimen of a DMARD, (disease modifying anti rheumatoid drugs).

4. Respiratory effects

- Therapeutic doses of salicylates stimulate respiration directly and indirectly; oxygen consumption and carbon dioxide production are increased, particularly in skeletal muscle.
 - This effect appears to be mediated by a salicylate-induced uncoupling of oxidative phosphorylation.
 - The increased carbon dioxide production stimulates respiration, but this is characterized by deep respirations rather than an increase in respiratory rate.
- High-doses result in medullary stimulation, leading to hyperventilation and a respiratory alkalosis. Compensation rapidly occurs because the kidney is able to increase the excretion of bicarbonate, producing a compensated respiratory alkalosis.
- Toxic doses or very prolonged salicylate administration can depress the medulla, resulting in an uncompensated respiratory acidosis. Because renal bicarbonate excretion is elevated and the salicylates cause the accumulation of organic acids, a metabolic acidosis also results.

5. Cardiovascular effects

- Therapeutic doses of salicylates have no significant cardiovascular effect; however, the prophylactic use of aspirin to reduce thromboembolic events in coronary and cerebral blood vessels are produced only at low doses (approx 1/2 the therapeutic dose) [Studies have demonstrated that such use results in long-term survival and reduced frequency of second myocardial infarctions.]
- High doses may cause peripheral vasodilatation by exerting a direct effect on smooth muscle.

- Toxic doses depress circulation directly and by central vasomotor paralysis. Non-cardiogenic pulmonary edema may occur in older patients on long-term salicylate therapy.

6. Gastrointestinal effects

- Salicylates can cause epigastric distress, nausea, and vomiting by irritating the gastric mucosal lining and stimulating the chemoreceptor trigger zone (CTZ) in the CNS.
- Salicylates, and NSAIDs in general, may cause a dose-related gastric ulceration, bleeding, exacerbation of peptic ulcer symptoms, and erosive gastritis.
 - Salicylates inhibit the formation of PGI₂ (prostacyclin), which inhibits gastric acid secretion and has a cytoprotective effect, especially on gastric mucosal cells.
 - Misoprostol is useful for the prevention of NSAID-induced gastric ulcers.
 - Salicylate-induced gastric bleeding is painless and may lead to an iron deficiency anemia.

7. Hepatic effects: Salicylate-related hepatic damage is usually mild, and reversible after discontinuation of therapy. Salicylates can produce at least two forms of hepatic injury.

- One form is dose-dependent and usually occurs in patients with connective tissue disorders. Usually, asymptomatic, elevated plasma transaminase levels (i.e., serum glutamic-oxaloacetic transaminase and serum glutamate pyruvate transaminase) are the key indications of hepatic insult damage.
- A second form of salicylate-induced hepatic injury is more severe and associated with the encephalopathy seen in Reye's syndrome.
 - This rare, and often fatal, disorder can occur with infection from varicella (chickenpox) virus and influenza virus.
 - Use of salicylates in children and even in adult with chickenpox or influenza is contraindicated.

8. Hematological effects

- Aspirin has no effect on leukocyte count, hemoglobin, or hematocrit at therapeutic doses. There is, however, a prolongation of bleeding time with doses as small as 300 mg of aspirin. This dose irreversibly inhibits platelet function for the 7-day (lifetime of the platelet).
- Because it can acetylate and inactivate cyclo-oxygenase, aspirin has important effects on the delicate balance between the initiation and the inhibition of platelet aggregation.
 - Platelets are ordinarily nonadherent. However, vascular injury and exposure to subendothelial

structures result in activation of the platelet cyclo-oxygenase enzyme system, leading to the production of TXA_2 , via thromboxane synthetase. TXA_2 can induce platelet aggregation.

- Concurrently opposing this physiologic process is the cyclo-oxygenase system, instead of thromboxane synthetase, vascular endothelial cells contain a prostacyclin synthetase, which converts the cyclo-oxygenase products PGG_2 and PGH_2 to PGI_2 , a potent inhibitor of platelet clumping.
- It is thought that aspirin in appropriate doses can preferentially inhibit the platelet cyclo-oxygenase system, blocking the formation of TXA_2 , thereby suppressing platelet clumping.
- By inhibiting initial platelet aggregation to sub-endothelial structures, aspirin also prevents the secondary release of adenosine diphosphate (ADP) from platelet granules, [a process that normally occurs when platelets clump]. *ADP release ordinarily brings about additional waves of platelet aggregation, leading to thrombus formation.* This effect persists 4-7 days after the drug has been discontinued.
- In doses greater than 6g/d, aspirin may reduce plasma prothrombin levels.
- Because of its effects on the blood, aspirin should be avoided in patients with severe hepatic disease, hypoprothrombinemia, vitamin K deficiency, or hemophilia.

9. Renal effects

- Salicylates decrease renal blood flow, resulting in salt and water retention, which increases circulating plasma volume (by about 20%) in patients taking large doses.
- In patients with congestive heart failure, impaired renal function, or hypovolemia, salicylates can further exacerbate renal dysfunction.
- The vasodilatory effects of PGI_2 on renal blood flow (and now glomerular filtration rate) may be more critical during impaired renal function.
- Salicylates also affect uric acid secretion, but the effect is dose-dependent: Low doses may decrease urate excretion whereas large doses may induce uricosuria.
- Small doses of salicylates may be enough to block the uricosuric action of probenecid and other agents that decrease tubular reabsorption of uric acid. *Salicylates should not be used concomitantly with uricosuric agents in the treatment of gout.*

10. Metabolic effects

- The salicylates uncouple oxidative phosphorylation.

- Large doses of the salicylates can produce hyperglycemia and glycosuria and can deplete liver and muscle glycogen.
- Aspirin, like other salicylates, can reduce lipogenesis by blocking the incorporation of acetates into fatty acids.
- Toxic doses can cause significant nitrogen loss, characterized by aminoaciduria.

11. Endocrine effects

- The salicylates, in very large doses, can stimulate steroid secretion by the adrenal cortex. This effect is mediated through action on the hypothalamus.
- Long-term salicylate therapy can decrease thyroidal uptake and clearance of iodine and can increase oxygen metabolism and the rate of disappearance of triiodothyronine (T_3) and thyroxine (T_4) from the circulation. These effects probably result from a competitive displacement of iodinated proteins from plasma proteins by salicylates.
- Use of salicylates may prolong the gestational period during pregnancy. This may be due to a delay in the onset of labor caused by the inhibition of PG synthesis in the uterus; PGs are believed to be involved in eliciting uterine contractions.

12. Immunological effects: In higher doses, salicylates suppress several antigen-antibody reaction including inhibition of antibody production, Ag-Ab aggregation and antigen induced release of histamine. These effects might also contribute to the beneficial effects in rheumatic fever.

13. Local effects: Salicylic acid when applied locally is a keratolytic. It also has mild antiseptic and fungistatic properties. Salicylic acid is also an irritant for the broken skin.

Therapeutic Indications

1. **As analgesic:** for treating headache, backache, myalgias, arthralgias, neuralgias, **toothache** and dysmenorrhea.
2. **Fever:** NSAIDs are useful for the symptomatic relief of fever.
3. **Inflammatory conditions:** Aspirin is effective in a number of inflammatory conditions such as arthritis and fibromyositis.
4. **Acute rheumatic fever:** In dose of 4-6 g/day (100 mg/kg/day) in 4-6 divided doses, aspirin brings about a dramatic relief of signs and symptoms in 24 to 48 hr.

338 SECTION – 11 Central Nervous System

The dose is reduced after 4-7 days and maintenance doses of 50 mg/kg/day are given for 2-3 weeks.

5. **Rheumatoid arthritis:** Aspirin relieves pain, reduces swelling and redness of joints in rheumatoid arthritis. Joint mobility improves, fever subsides, and there is a reduction in morning stiffness. But NSAIDs do not alter the progress of the disease. The relief is only symptomatic.
 - Dose 4-6 g/day in 4-6 divided doses.
6. **Osteoarthritis:** It provides symptomatic relief in osteoarthritis.
7. **Postmyocardial infarction and post stroke:** Aspirin inhibits platelet aggregation-and this may lower the incidence of re-infarction-in a low dose of 50 to 300 mg/day. It also decreases the incidence of transient ischemic attacks (TIA) and stroke in such patients.
8. **Miscellaneous uses**
 - To delay labor – since PGs are involved in the initiation of labor, aspirin delays labor due to PG synthesis inhibition.
 - Some studies suggest that long-term use of aspirin at low doses is associated with a lower incidence of colon cancer.
 - Patent Ductus Arteriosus. Aspirin may bring about closure of PDA in the newborn.

9. **Local:** Salicylic acid is used as a keratolytic, fungistatic and mild antiseptic.

- * Methylsalicylate is a counter-irritant used in myalgias.

Preparations and administration (see Table 11.11.1)

- Aspirin is available as tablets, capsules, and suppositories in a wide range of dosages.
 - Rectal administration may be required in infants or if oral administration is impossible.
 - Buffered or enteric-coated aspirin preparations may be better-tolerated.
- **Nonacetylated salicylates:** Such as sodium salicylate, and choline magnesium salicylate, appear to cause less gastric irritation and have less effects on platelet function than aspirin. Although they may be safer than acetylated salicylates for aspirin-sensitive patients, they may not be as effective.
- **Diflunisal:** It is a salicylate that can be taken twice daily. It has four times the potency of aspirin when used in the treatment of osteoarthritis or musculoskeletal pain.
- **Mesalamine (5-aminosalicylic acid):** It is used for inflammatory bowel disease; it has poor oral absorption and, thus, is used for its local effect in rectal preparations.

Table 11.11.1: Dosage and preparation of salicylates

Drug	Preparation	Dose
Aspirin	300, 350 tab; DISPRIN (Aspirin 350 mg and Calcium carbonate 105 mg)	Analgesic—300-600 mg every 6-8 hr Anti-inflammatory—4-6 gm/day Antiplatelet effects—75-300 mg/day
Sodium salicylate	325, 650 mg tablets	325-650 mg every 4-8 hr
Salicylic acid	2% ointment; Whitfield's ointment: – Salicylic acid 3% – Benzoic acid 6%	for topical use
Methylsalicylate	Ointment/liniment (Oil of wintergreen)	As counter irritant for topical use
Diflunisal	250, 500 mg tab (DOLOBID)	250 mg every 8-12 hr

Adverse effects

- **Common one are** Nausea, epigastric distress, vomiting, erosive gastritis, peptic ulcer, increased occult blood loss in stools, etc.
- **Uncommon:** Allergic reactions (1 in 500 patients): manifested as rashes, urticaria, rhinorrhea, angioedema, and asthma especially in those with a history of allergies.
- As aspirin inhibits only cyclo-oxygenase pathway, arachidonic acid is available for conversion by lipoxygenase pathway into leukotrienes. Leukotrienes are powerful bronchoconstrictors. Hence **aspirin can precipitate bronchial asthma** in some individuals. Of the currently available NSAIDs, diclofenac and indomethacin inhibit the synthesis of both PGs and LTs.
- Salicylates can cause **hemolysis** in patients with G₆PD deficiency.
- **Nephrotoxicity:** Almost all NSAIDs can cause nephrotoxicity after long-term use.
- **Hepatotoxicity** can also occur.
- **Reye's Syndrome:** Seen in children is a form of hepatic dysfunction which may be fatal. It develops a few days after a viral infection especially influenza and varicella. An increased incidence of this syndrome has been noted when aspirin is used to treat fever. **Hence, aspirin is contraindicated in children with viral fever.**
- **Pregnancy and infancy:** Aspirin when taken at full term delays the onset of labor due to inhibition of PG synthesis (PGs play an important role in the initiation of labor).
- **Premature closure of ductus arteriosus** may occur in the fetus resulting in portal hypertension. It can also increase postpartum bleeding due to inhibition of platelet aggregation.

Chronic Salicylate Poisoning

- **Salicylism:** Prolonged administration of salicylates as in the treatment of rheumatoid arthritis may lead to chronic salicylate intoxication termed '**salicylism**'.
- The syndrome is characterized by headache, vertigo, dizziness, tinnitus, vomiting, mental confusion, diarrhea, sweating, difficulty in hearing, thirst and dehydration.
- These symptoms are reversible on withdrawal of salicylates.

Acute salicylate intoxication:

- Poisoning may be accidental or suicidal. It is more common in children, 15-30g is the fatal dose of aspirin.

• **Symptoms and signs of Salicylate intoxication:**

- **Mild intoxication:** from aspirin or other salicylates. Characteristic findings include:
 1. Headache, mental confusion, lassitude, and drowsiness
 2. Tinnitus and difficulty in hearing
 3. Hyperthermia, sweating, thirst, hyperventilation, vomiting, and diarrhea
- **More severe:** Salicylate intoxication can result in more severe CNS disturbances, including hallucinations, vertigo, or convulsions. In addition, skin eruptions and, more important, marked alterations in acid-base balance are observed.
- **Fatal intoxication:** Can be produced in children by ingestion of as little as 10 g of aspirin or as little as 5 g of methyl salicylates, which is widely used as a counterirritant in liniments and has the characteristic odor and taste of wintergreen.

Treatment of salicylates poisoning includes:

- Gastric lavage to eliminate unabsorbed drugs.
- IV fluids to correct acid-base imbalance and dehydration.
- Temperature is brought down by external cooling with alcohol or cold water sponges.
- If hemorrhagic complications are seen, blood transfusion and vitamin K are needed.
- The IV fluids contain Na⁺, K⁺, HCO₃⁻ and glucose (to treat hypokalemia and acidosis). Blood pH should be monitored.
- In severe cases, forced alkaline diuresis with sodium bicarbonate and a diuretic like furosemide is given along with IV fluids. Sodium bicarbonate ionizes salicylates making them water soluble and enhances their excretion through kidneys.

Precautions and contraindications: Peptic Ulcer, liver diseases, bleeding tendencies, children suffering from viral fever and pregnancy are contraindications for the use of salicylates. Treatment with NSAIDs should be stopped one week before any surgery.

Drugs interactions

- In low doses salicylates can counter the uricosuric actions of probenecid by decreasing uric acid excretion.
- Salicylates compete for protein – binding sites and displace drug molecules resulting in toxicity with warfarin, heparin, naproxen, phenytoin and sulfonylureas. Inhibition of platelet aggregation may increase the risk of bleeding with oral anticoagulants.

Acetaminophen

Chemistry

- A para-aminophenol derivative, acetaminophen is the major active metabolite of phenacetin.
- Phenacetin was the first drug used in this group. But, due to severe adverse effects it is now banned.
- **Paracetamol**, acetaminophen a metabolite of phenacetin is found to be safer and effective.

Pharmacokinetics

- **Absorption:** Acetaminophen is completely and rapidly absorbed from the gastrointestinal tract, with peak plasma levels reached within 30-60 minutes. The plasma half-life is about 2 hours.
- **Metabolism and excretion:** About 3% is excreted unchanged in the urine, and 80%-90% is conjugated with glucuronic or sulfuric acid in the liver and then excreted in the urine within the first day.
 1. Small amounts of hydroxylated metabolites are ordinarily excreted.
 2. At high doses, one of these metabolites undergoes spontaneous dehydration to form N-acetyl-p-benzoquinone, the product thought to be responsible for hepatotoxicity.

Pharmacological effects

- **Analgesic and antipyretic effects:** Acetaminophen is as effective as aspirin, is similar in potency, and in single analgesic doses, has the same time-effect curve. However, acetaminophen has no anti-inflammatory activity, for reasons that are not completely understood. Acetaminophen appears to be an inhibitor of PG synthesis in the brain, thus accounting for its analgesic and antipyretic activity; but it is much less effective than aspirin as an inhibitor of the peripherally located PG biosynthetic enzyme system that plays such an important role in inflammation.
- Acetaminophen exerts little or no pharmacological effect on the cardiovascular, respiratory, or gastrointestinal systems, on acid-base regulation, or on platelet function.

Therapeutic uses

- Acetaminophen provides an effective alternative when aspirin is contraindicated (e.g., in patients with peptic ulcer or hemophilia) and when the anti-inflammatory action of aspirin is not required.
- Acetaminophen has virtually replaced the formerly popular phenacetin because of the renal toxicity ascribed to the later drug. However, acetaminophen, the main metabolite of phenacetin, is also associated with renal toxicity in a dose-dependent manner.

- Paracetamol is used as an analgesic in painful conditions like **toothache**, headache and myalgia.
- As an antipyretic.
- **Chronic pulpitis, periodontal abscess, post-extraction**—paracetamol is used with ibuprofen.

Preparations and administration: Acetaminophen is available in tablet and liquid form and is administered orally.

Adverse effects

- At therapeutic doses, acetaminophen is well tolerated; however, adverse effects include:
 - Skin rashes and drug fever (hyperpyrexia caused by an allergic reaction to the drug).
 - Rare instances of blood dyscrasias.
 - Renal tubular necrosis and renal failure.
 - Hypoglycemic coma.
- An overdose of acetaminophen (about 15 g in an adult; about 4 g in a child) can result in severe hepatotoxicity, resulting in centrilobular hepatic necrosis. Doses greater than 20 g are potentially fatal.
 - The toxic metabolite of acetaminophen appears to be inactivated in the liver by glutathione.
 - It is thought that when glutathione stores are consumed, the N-acetyl-p-benzo-quinone metabolite binds covalently to cellular constituents, producing **hepatocellular** damage.
 - a. **Manifestations** are seen within 2-4 days and include increased serum transaminase, jaundice, liver tenderness, and prolonged prothrombin time which may progress to liver failure in some patients. Hepatic lesions are reversible when promptly treated.
 - b. *Chronic alcoholics and infants are more prone to hepatotoxicity.*
 - Although clinical symptoms such as nausea and vomiting occur during the first 24 hours after toxic ingestion, signs of hepatic damage (e.g., enzyme abnormalities) may not occur for 2-6 days.
 - **Treatment consists of:**
 - a. Stomach wash should be given.
 - b. Activated charcoal prevents further absorption.
 - c. Antidote is N-acetylcysteine (150 mg/kg IV infusion over 15 min repeated as required; oral loading dose: 140 mg/kg followed by 70 mg/kg every 4 hourly: 18 doses); more effective when given early.
 - d. Administration of N-acetylcysteine partly replenishes the glutathione stores of the liver and prevents binding of toxic metabolites to the cellular constituents.

- e. Hemodialysis, if begun within the first 12 hours after ingestion.

PYRAZOLON DERIVATIVES

Phenylbutazone

Chemistry: Phenylbutazone, derived from pyrazolon, is a congener of antipyrène.

Pharmacokinetics: Phenylbutazone is rapidly and completely absorbed, with peak plasma levels reaching within 2 hours. The half-life is notably long, 50-65 hours. It is 98% bound to plasma proteins. Significant concentrations may persist in synovial fluid for up to 3 weeks after treatment.

Pharmacological effects

- Phenylbutazone is an effective anti-inflammatory agent, but toxicity prohibits its long-term use.
- Phenylbutazone possesses anti-inflammatory and analgesic activity that is qualitatively similar to that of aspirin. Its analgesic effect against nonrheumatic pain, however, is less than that of aspirin.

Therapeutic uses

- Because phenylbutazone is poorly tolerated by many patients, it is not used as an antipyretic or general analgesic agent.
 - Phenylbutazone is chiefly used in the short-term therapy of acute gout and in acute exacerbations of rheumatoid arthritis, but only after other agents have failed.
 - Brief courses of the drug may be beneficial in the treatment of osteoarthritis and ankylosing spondylitis.

Dose: 100-200 mg, BD. Small doses may be given 3-4 times a day to avoid gastric irritation.

Administration: Phenylbutazone is administered orally. It should be taken with meals to lessen gastric irritation and damage.

Adverse effects

- Phenylbutazone is more toxic than aspirin and is poorly tolerated – dyspepsia, epigastric distress, nausea and vomiting are common. **Peptic ulceration and diarrhea may occur.** Edema is a limiting factor and may precipitate CCF.
- Hypersensitivity reactions like rashes, serum sickness, stomatitis, hepatitis, nephritis, dermatitis and jaundice can occur. Phenylbutazone may cause serious **hematological complications** such as bone marrow

depression, aplastic anemia, agranulocytosis and thrombocytopenia.

- It may inhibit iodine uptake by thyroid resulting in **hypothyroidism and goiter** on long-term use.
- CNS effects like insomnia, vertigo, optic neuritis, blurring of vision and convulsions may be encountered. *Because of its toxicity, phenylbutazone is withdrawn from market in many western countries.*

Therapeutic indications

- Rheumatoid arthritis
- Ankylosing spondylitis
- Osteoarthritis
- Produces satisfactory relief from pain and inflammation in acute attacks of Gout.
- Other musculoskeletal disorders.

Drug interactions

- Phenylbutazone may displace:
 - Oral anticoagulant drugs
 - Oral hypoglycemic drugs
 - Sulfonamides
 - Protein-bound thyroid hormone, thus complicating interpretations of thyroid function tests
- Induction of hepatic enzymes, or mixed function oxidases (MFOs), can disturb the metabolism of other active moieties.
- The effects of insulin may be potentiated by phenylbutazone.

Azapropazone: It is structurally related to phenylbutazone but is less likely to cause agranulocytosis; $t_{1/2}$ is 12-16 hourly.

Metamizol: It is a potent analgesic and antipyretic, but poor anti-inflammatory agent and has no uricosuric properties (ANALGIN, NOVALGIN) 500 mg 3-4 times a day. It offers no advantages over aspirin. Not recommended in children up to 6 years. Sold in market as OTC drug. (over the counter)

Propiphenazone

- It is similar to metamizol.
- Dose: 300-600 mg 3-4 times a day (SARIDON).

INDOLE ACETIC ACID DERIVATIVES

Indomethacin

Chemistry: Indomethacin is a methylated indole derivative.

Pharmacokinetics

- **Absorption** from the gastrointestinal tract is rapid and virtually complete, with peak plasma levels reached in

approximately 2 hours. As with other drugs, absorption may be delayed when taken with meals.

- **Distribution**
 - Indomethacin is 90% bound to plasma proteins and exhibits extensive tissue binding.
 - **Concentration of indomethacin in synovial fluid is equal to plasma levels within 5 hours of administration.**
- **Metabolism:** Indomethacin is largely inactivated by O-demethylation (approximately 50%) and glucuronidation (approximately 10%).

Pharmacological effects

- Indomethacin has prominent anti-inflammatory, antipyretic, and analgesic activity.
 - Although indomethacin is a more potent anti-inflammatory agent than aspirin, the doses of indomethacin that are well tolerated by patients with rheumatoid arthritis do not show superior results compared with the salicylates.
 - There is evidence for both a central and peripheral action.

Therapeutic uses

- Because of its toxicity and side effects, indomethacin is not routinely used for analgesia or antipyresis.
 - The major uses of indomethacin are in the treatment of **rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and acute gout.**
 - It has also been used in the treatment of **patent ductus arteriosus** in neonates, and in the treatment of **Bartter's syndrome** (juxtaglomerular cell hyperplasia), characterized by hypokalemic alkalosis, hyperaldosteronism, and normal blood pressure despite high renin blood levels.

Administration

- Indomethacin usually is administered orally. It should be taken with meals to lessen gastric irritation.
- An intravenous solution is available for treating patent ductus arteriosus.

Adverse effects: Overall, 35%-50% of all patients receiving indomethacin report some adverse effect; approximately 20% must discontinue therapy. Most adverse effects are dose-related.

- **Gastrointestinal complaints include:**
 1. Anorexia, nausea, and abdominal pain
 2. Ulcers, sometimes with perforations and hemorrhage
 3. Diarrhea, sometimes associated with ulcerative lesions of the lower gastrointestinal tract
 4. Pain caused by decreased mesenteric blood flow

- **CNS effects, which are the most frequently reported, includes:**

1. Severe frontal headache (25%-50%)
2. Dizziness and vertigo
3. Mental confusion
4. Severe depression, psychosis, hallucination, and suicide

- **Hematological reactions:** such as neutropenia, thrombocytopenia, impaired platelet function, and rarely, aplastic anemia

- **Hypersensitivity reactions:** such as rashes, itching, urticaria, and acute asthma (aspirin-sensitive patients may exhibit cross-reactions to indomethacin)

Contraindication

- Pregnant or nursing women (indomethacin crosses the placenta freely, which can result in constriction of the fetal ductus arteriosus and oligohydramnios as a result of decreased fetal urine output)
- Patients with psychiatric disorders
- Patients with epilepsy
- Patients with parkinsonism
- Patients with renal disease
- Patients with gastrointestinal ulcerative lesions
- Machine operators

Drug interactions

- Indomethacin does not appear to alter the uricosuric effects of probenacid. It is routinely used in the treatment of gout.
- Indomethacin does not appear to modify the effect of oral anticoagulants, but concurrent administration could be hazardous because of increased potential for gastrointestinal bleeding.
- Indomethacin does antagonize the natriuretic and antihypertensive effects of furosemide, thiazide diuretics, β -adrenergic blocking agents, and angiotensin converting enzyme (ACE) inhibitors.

Sulindac

Chemistry: Structurally, sulindac is an indene-derived NSAID and is closely related to indomethacin.

Pharmacokinetics

- **Absorption:** Approximately 90% of the drug is absorbed after oral administration, with peak plasma levels of sulindac and its sulfide metabolite occurring at 1 hour and 2 hours, respectively.
- **Half life period:** Sulindac and its major metabolites are all extensively bound to plasma proteins. The half-life of sulindac is approximately 7 hours, but the sulfide metabolite half-life is approximately 18 hours.

- **Excretion:** Urine and feces are principal routes of excretion.

Pharmacological effects

- Sulindac is an anti-inflammatory, analgesic, and antipyretic drug with a relative strength of approximately half of indomethacin's potency.
- Sulindac is a prodrug. Its sulfide metabolite is more than 500 times more potent (than sulindac) as an inhibitor of cyclo-oxygenase.

Therapeutic uses: Sulindac is primarily used in the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and acute gout.

Administration: It is given orally.

Adverse effects

- Sulindac has a lower incidence of toxicity as compared with indomethacin.
 - Gastrointestinal effects occur in about 20% of patients, although the reactions are generally mild.
 - There are reports of cross-reactivity to sulindac in aspirin-sensitive patients. Skin rash and pruritus can occur in approximately 5% incidence.
 - Platelet function may be impaired, and bleeding time is prolonged.
 - Sulindac does not appear to be “renal-sparing” and should be used cautiously in patients with compromised renal function.

ARYL ACETIC ACID DERIVATIVE

Diclofenac

Chemistry: Diclofenac is the first of a series of phenylacetic acid derivatives developed as anti-inflammatory agents.

Pharmacokinetics

- Oral absorption is rapid and complete, with peak plasma levels achieved within 2 hours.
- There is a substantial first-pass effect, reducing systemic levels by as much as 50%.
- Diclofenac is highly protein-bound in plasma, and its half-life is 1-2 hours.
- Diclofenac accumulates in synovial fluid, which may account for its long-lived therapeutic effect, despite its short plasma half-life.

Pharmacological effects

- Diclofenac is a potent anti-inflammatory, antipyretic, and analgesic agent; it is a more potent inhibitor of cyclo-oxygenase than indomethacin or naproxen.

- Additionally, diclofenac appears to alter the release or uptake of fatty acids, reducing intracellular levels of arachidonate in leukocytes.

Therapeutic uses

- Diclofenac is approved for use in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.
- It may also be useful for short-term treatment of acute musculoskeletal injury, tendinitis, bursitis, postoperative pain, and dysmenorrhea.

Adverse effects

- Approximately 30% of diclofenac patients report an adverse event, with about 2% discontinuing therapy.
 - Gastrointestinal symptoms (20%) are the most common; bleeding, ulceration, and perforation have been reported.
 - Elevated hepatic transaminase levels occur in about 15% of diclofenac patients. Hepatic transaminases should be monitored for the first 8 weeks of therapy. Hepatitis and jaundice have been reported.
 - Diclofenac is not recommended for children, nursing mothers, or women who are pregnant.

Ketorolac

Chemistry: Ketorolac is a member of the pyrrole group of NSAIDs.

Pharmacokinetics

1. **Absorption:** Ketorolac is completely absorbed following intramuscular injection and reaches peak plasma concentrations in 1 hour.
2. It is highly protein-bound and has a terminal half-life of 4-6 hours.
3. **Excretion:** Ketorolac is excreted in the urine.

Therapeutic indications: Ketorolac is as effective as morphine or meperidine for the short-term relief of moderate to severe pain. Unlike narcotic analgesics, ketorolac does not produce respiratory depression.

Adverse effects

- They are similar to those associated with the short-term use of oral NSAIDs (e.g., drowsiness, dyspepsia, gastrointestinal pain and nausea). Serious gastrointestinal bleeding has not been reported.
- It is mostly used parenterally though it can also be given orally.

PROPIONIC ACID DERIVATIVES

• Propionic acid derivatives include:

1. Ibuprofen
 2. Naproxen
 3. Fenoprofen
 4. Ketoprofen
 5. Flurbiprofen
 6. Oxaprozin
- Ibuprofen is better tolerated than aspirin. Analgesic, antipyretic and anti-inflammatory efficacy is slightly lower than aspirin.
 - It is 99% bound to plasma proteins.
 - These agents offer significant advantages over aspirin and indomethacin because they are better tolerated at anti-inflammatory doses.
 - All of these compounds can induce gastrointestinal side effects or alter platelet function; some may alter leukocyte function and motility.

Drug interactions

1. Potential adverse drug interactions may result from the high degree of plasma albumin binding.
2. Propionic acid derivatives may reduce the diuretic and natriuretic effects of furosemide, as well as the antihypertensive effects of thiazides, adrenergic antagonists, and ACE inhibitors.

Ibuprofen

Pharmacokinetics: Oral absorption is rapid, with peak plasma levels occurring within 1-2 hours and a half-life of about 2 hours. Excretion is rapid and complete, with more than 90% appearing in the urine, mostly as metabolites or conjugates.

Pharmacological effects: Ibuprofen is equal to aspirin in its anti-inflammatory effect, but it is a more effective analgesic than aspirin or acetaminophen.

Therapeutic indications: As an NSAID, ibuprofen is used for the treatment of arthritis and osteoarthritis.

Adverse effects

- Gastrointestinal effects occur in approximately 5%-15% of patients, but the incidence of these events is less than with aspirin or indomethacin. Nevertheless, ibuprofen should be used cautiously in patients with known peptic ulceration or gastric intolerance to other aspirin-like drugs.
- Ibuprofen should not be used during pregnancy or nursing women.
- Ibuprofen is a potent inhibitor of cyclo-oxygenase and prolongs bleeding time.

Naproxen

Pharmacokinetics

- Absorption: Peak concentrations achieved within 2-4 hours, but naproxen's half-life is approximately 14 hours, permitting twice-a-day dosing.
- Distribution: Naproxen is highly bound to plasma proteins. It does cross the placenta and appears in the milk of lactating women at about 1% of the maternal plasma level.
- Excretion is primarily in the urine.

Therapeutic uses: As an NSAID, naproxen is used for the treatment of rheumatoid arthritis and osteoarthritis.

Adverse effects

- Whereas the incidence of gastrointestinal and CNS effects approximates those of indomethacin, Naproxen is more efficacious and better tolerated.
- Less common are pruritus and dermatological problems.
- Isolated cases of jaundice, renal dysfunction, angioneurotic edema, thrombocytopenia, and agranulocytosis have been reported.

Fenoprofen

Pharmacokinetics

- Oral absorption is rapid, although not as complete (85%) as for ibuprofen; peak plasma levels occur at approximately 2 hours, with a half-life of approximately 3 hours.
- Similarly, there is a high degree of plasma protein binding and virtually complete elimination via the urine.

Adverse effects

- GI effects account for the majority (15%) of reports, but these are generally milder than with equal doses of aspirin, and discontinuation is rarely required.
- CNS effects include tinnitus, vertigo, lassitude, confusion, and anorexia.

Ketoprofen

Pharmacokinetics: Ketoprofen exhibits a profile similar to that of ibuprofen, with a slightly longer half-life in elderly patients.

Therapeutic uses: Like ibuprofen, ketoprofen is used to treat arthritis and osteoarthritis. It is also approved for ophthalmic use to relieve itching associated with seasonal allergic conjunctivitis.

Adverse effects

- Gastrointestinal effects (30%) are generally less severe than those seen with aspirin and may be reduced further by taking the drug with food, milk, or antacids.

- Renal function should be monitored in patients older than 60 years of age or with impaired renal function because ketoprofen can cause fluid retention and transient increases in plasma creatinine levels.
- Patients treated concurrently with ketoprofen and methotrexate can develop life-threatening methotrexate hepatotoxicity.

Flurbiprofen

Pharmacokinetics. Flurbiprofen has a profile similar to that of ibuprofen, but its plasma half-life is approximately 6 hours.

Therapeutic uses

- Flurbiprofen tablets are used to treat the signs and symptoms of rheumatoid arthritis and osteoarthritis.
- Flurbiprofen is available in an ophthalmic dosage form for the treatment of postoperative miosis.
 - Trauma during intraocular surgery releases PGs, which cause progressive miosis.
 - Flurbiprofen decrease miosis without affecting intraocular pressure.

Adverse effects

- The profile is similar to that of other propionic acid derivatives with regard to the incidence of gastrointestinal and CNS effects.
- Flurbiprofen may exacerbate herpes simplex keratitis and delay wound healing. A foreign body sensation is the most common adverse effect.

Oxaprozin

Pharmacokinetics

- Oxaprozin is orally absorbed and reaches peak serum concentrations in 3-5 hours.
- It is metabolized in the liver and excreted in bile and urine.
- The elimination half-life is 50-60 hours and increase with the patient's age.

Therapeutic uses

- Oxaprozin is comparable in effectiveness to ibuprofen and other NSAIDs for treatment of rheumatoid arthritis or osteoarthritis.
- Its long half-life permits once-a-day dosing.

Adverse effects

- The incidence of gastrointestinal side effects may be slightly higher than for ibuprofen.
- Renal toxicity, hepatic toxicity, and prolonged bleeding may occur.

Etodolac

Chemistry. Etodolac is a pyranone acid derivative.

Pharmacokinetics

- Absorption. Etodolac is well absorbed orally; it reaches a peak serum concentration in 1-2 hours.
- Distribution. More than 99% of etodolac is bound to plasma proteins.
- Metabolism and excretion. Etodolac is metabolized in the liver and excreted in the urine. Its elimination half-life is 6-7 hours.

Therapeutic uses: Etodolac is used in the treatment of osteoarthritis and as an analgesic.

Adverse effects: It include abdominal pain and dyspepsia. Gastrointestinal ulceration occurs in less than 0.3% of patients.

ANTHRANILIC ACID DERIVATIVES

Fenamates: Mefenamic acid and meclofenamate

Chemistry

- Mefenamic acid and meclofenamate are both N-substituted phenylanthranilic acids.
- Other chemical members of this family include flufenamic, tolfenamic, and etofenamic acids.

Pharmacokinetics

- Peak plasma levels for mefenamic acid and meclofenamic acid are reached at approximately 2 hours and 2-4 hours, respectively.
- Plasma half-lives for these drugs are about 2-4 hours, with more than 50% elimination in the urine.

Pharmacological effects: The fenamates are anti-inflammatory, analgesic, and antipyretics.

Therapeutic uses

- Mefenamic acid is primarily used as an analgesic in rheumatoid arthritis, soft-tissue injury, and dysmenorrhea. Toxicity limits its usefulness, and it appears to have no advantage over other analgesic agents.
- As anti-inflammatory agents, the fenamates have been used in short-term trials for osteoarthritis and rheumatoid arthritis but, again, offer no clear advantage over other NSAIDs.

Adverse effects

- The most commonly reported adverse effects involve the gastrointestinal system and include dyspepsia or general discomfort.
 - Diarrhea, which may be severe and associated with steatorrhea or bowel inflammation, is also common.

- The fenamates are contraindicated in patients with a history of gastrointestinal disease.
- Hemolytic anemia is a serious side effect and may be of an autoimmune origin.
- There are reports of cross-reactivity to fenamates in aspirin-sensitive patients.

OXICAMS

Piroxicam

Chemistry: Piroxicam is one of the oxicam derivatives, a class of enolic acids.

Pharmacokinetics

- Oral absorption is virtually complete, with peak plasma level occurring 3-5 hours after dosing.
 - The plasma half-life is estimated to be approximately 50 hours, which allows once daily dosing.
 - Steady-state plasma levels are achieved within 7-12 days, and maximal therapeutic responses occur within 2 weeks.

Pharmacological effects

- As an anti-inflammatory agent, piroxicam is equipotent to indomethacin, aspirin, and naproxen. Piroxicam may inhibit activation of neutrophils, suggesting an additional mode of anti-inflammatory action.
- As with other cyclooxygenase inhibitors, piroxicam is both analgesic and antipyretic.

Therapeutic uses

- Piroxicam is approved for use in the treatment of rheumatoid arthritis and osteoarthritis.
- It has also been used in ankylosing spondylitis, musculoskeletal disorders, dysmenorrhea, postoperative pain, and gout.

Adverse effects

- Gastrointestinal side effects are most common. The longer half-life of piroxicam may cause a higher incidence of gastrointestinal bleeding than other NSAIDs.
- Piroxicam may have cross-reactivity in patients who are aspirin-sensitive.

ALKANONES

Nabumetone

Chemistry: Nabumetone is a naphthoquinone.

Pharmacokinetics

- Nabumetone is absorbed in the duodenum as nabumetone, a weak cyclooxygenase (COX-2) inhibitor, and

converted in the liver to 6-MNA, a strong cyclooxygenase inhibitor.

- Peak serum concentrations of 6-MNA occur in 5 hours, with a terminal half-life of 24 hours.

Therapeutic uses: Nabumetone is effective for the treatment of rheumatoid arthritis and osteoarthritis.

Adverse effects

- As an inactive prodrug, nabumetone may cause less local gastric irritation.
- Gastrointestinal, CNS, and photosensitive adverse reactions occurs.

SULFONANILIDE DERIVATIVES

Nimesulide

- A sulfonamide compound is a weak inhibitor of PG synthesis with a higher affinity for COX-2 than COX-1.
- It inhibits leukocyte function, prevents the release of mediator and in addition has **antihistaminic and antiallergic properties**.
- **Actions:** Nimesulide has analgesic, antipyretic and anti-inflammatory actions like other NSAIDs.
- **Pharmacokinetics:** Nimesulide is well-absorbed orally, extensively bound to plasma proteins and has a $t_{1/2}$ of 3 hours. It is excreted by the kidney.
- **Dose:** 50-100 mg BD

Adverse effects: They are mild; and induces nausea, epigastric pain, rashes, drowsiness and dizziness. It is claimed to be better tolerated. Long-term use can cause hepatotoxicity.

Therapeutic uses

- Nimesulide is used as an analgesic, antipyretic and anti-inflammatory agent for short periods as in headache, toothache, myalgia, dysmenorrhea, sinusitis, postoperative pain and arthritis.
- It is beneficial in patients who develop bronchospasm with other NSAIDs.

Celecoxib

- A sulfonamide, is a highly selective COX-2 inhibitor.
- It is an effective anti-inflammatory agent useful in rheumatoid arthritis and osteoarthritis.
- Early studies have shown it to be less ulcerogenic with other adverse effects are similar to NSAIDs. It does not affect platelet aggregation. **Rofecoxib** has properties similar to celecoxib.
- Nabumetone and Valdecoxib are recently developed selective COX-2 inhibitors.

Tolmetin**Pharmacokinetics**

- Tolmetin is rapidly and completely absorbed from the gastrointestinal tract.
- Peak plasma levels are achieved within 20-60 minutes after dosing, and the plasma half-life is about 5 hours.
- Tolmetin is extensively bound to plasma proteins and excreted virtually completely in the urine.

Pharmacological effects

- Tolmetin is an NSAID that is more potent than aspirin but less potent than indomethacin.
- It is thought to preferentially inhibit CNS cyclooxygenase.
- Tolmetin also produces analgesic and antipyretic effects.

Therapeutic uses: The major therapeutic indication for tolmetin is for the treatment of juvenile rheumatoid arthritis, adult rheumatoid arthritis, and osteoarthritis.

Adverse effects

- They are those common to most of the other NSAIDs including:
 - Gastrointestinal discomfort
 - CNS symptoms
 - Cross-reactivity in aspirin-sensitive patients
 - Anaphylactoid reactions in some patients who are not aspirin-sensitive.

Antagonists of Leukotriene Synthesis and Leukotriene Receptors**Zileuton, docebenone, piroprost**

- Some of them inhibit 5-lipoxygenase preventing the synthesis of leukotrienes, while others act as competitive antagonists of LT receptor.

- They are useful in asthma and other inflammatory conditions.
- **Adverse effects:** Dyspepsia, diarrhea and headache.

Drugs that Block both Cyclo-Oxygenase and Lipoxygenase

They are tenidap, diclofenac and indomethacin. Tenidap also blocks IL-1 formation.

Advers effects

- They are milder and the incidence is lower.
- Nausea, vomiting, gastric discomfort, CNS effects, hypersensitivity reactions, fluid retention are all similar but less severe.

Dose: Ibuprofen – 400-800 mg TDS (BRUFEN) ibuprofen + paracetamol (COMBIFLAM)

Therapeutic indication

- As an analgesic in painful conditions.
- In fever.
- Soft tissue injuries, fractures, following tooth extraction, to relieve postoperative pain, dysmenorrhea and osteoarthritis.
- Gout.
- Chronic pulpitis, periodontal abscess, gingival abscess – a combination of ibuprofen with paracetamol is preferred.
- Surgical removal of impacted tooth—a combination of ibuprofen with a skeletal muscle relaxant like chlorzoxazone is recommended.

Drugs Used in Rheumatoid Arthritis and Gout

Definition: Rheumatoid arthritis (RA) is a chronic, progressive, **autoimmune, crippling inflammatory disorder**, mainly affecting the joints and the periarticular tissues.

- The antigen-antibody complex triggers the pathological process of rheumatoid arthritis.
- Mediators of inflammation released in the joints initiate the inflammatory processes.
- There is local synthesis of leukotrienes (IL-1) and prostaglandins.
- IgM: activate RF/complement (*chemotactic for neutrophils*)
- The earliest lesion is vasculitis, followed by synovial proliferation and edema and infiltration with inflammatory cells (neutrophils).
- Prostaglandins cause vasodilation and pain.
- The inflammatory cells also release; *lysosomal enzymes which cause erosion and damage to bones and cartilages.*

Drugs used in the Treatment of Rheumatoid Arthritis

Ist line of drug

1. **NSAIDs** [Nonsteroidal anti-inflammatory drugs]
[They afford only symptomatic relief and are not the disease modifying drug]

IIInd line of drugs

1. **DMARDs** [Disease modifying Anti-rheumatoid Drugs] or DMDs or **SAARDs** [Slow Acting Anti-rheumatoid Drugs].
= Gold, d-penicillamine, Chloroquine and Hydroxy-chloroquine, Sulphasalazine, TNF blocking drugs
[Take months for its action to appear]
2. **Immunosuppressants:** Methotrexate, Cyclophosphamide, Azathioprine, Leflunomide, cyclosporine, etc.
3. **Adjuvants:** Glucocorticoids

General Considerations

- DMARDs interfere with the pathogenesis of rheumatoid arthritis.
- DMARDs are generally not the first line drugs used to treat patients with arthritis. but, Because degenerative lesions do not regress once formed, there is an increasing tendency to institute DMARD therapy early in progressive cases.
- Combination therapy with second-line agents has generally failed to be beneficial.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Nonsteroidal anti-inflammatory drugs are the first line drugs in RA.
- NSAIDs may provide symptomatic relief for joint pain and morning stiffness, but they do not modify the course of the disease. Occult joint damage may still be occurring.

Disease Modifying Drugs (DMDs) or (DMARDs)

- Disease modifying drugs are also called *disease modifying anti-rheumatic drugs* (DMARDs).
- These are the **second line drugs** and are reserved for patients with progressive disease who do not obtain satisfactory relief from NSAIDs. They are capable of arresting the progress of the disease and inducing remission in these patients.
- Recent studies have shown that RA causes significant systemic effects that shorten life expectancy. This has renewed interest in the use of DMDs in RA. The beneficial effects of these drugs may appear up to 6 months and are therefore called **Slow Acting Anti-rheumatic Drugs (SAARDs)**.

Gold Salts

- They were introduced for the treatment of RA in 1929, but their beneficial effects were clearly shown only in 1950s
- On treatment, a gradual reduction of the signs and symptoms are seen along with a decrease in the rheumatoid factor and immunoglobulin.

Chemistry: Commonly used gold preparations are aurous salts in which the gold is attached to sulfur.

Pharmacokinetics

- Aurothioglucose and gold sodium thiomalate are given by intramuscular injection.
 - Peak plasma levels occur within 2-6 hours, and virtually all (95%) is protein bound.
 - The plasma half-life is about 7 days for a 50-mg dose.
- Auranofin is given orally with about 25% absorption. Steady-state concentration is achieved within 8-12 weeks of treatment.
 - A 6-month regimen of 6 mg / day yields about 20% gold accumulation as compared with injectable gold compounds.
 - With auranofin, the half-life of gold in the body is about 80 days.
- With long-term chrysotherapy, gold get deposited in the body. Gold can be detected in the urine up to 1 year after cessation of chrysotherapy.

Mechanism of action

- Gold preparations (i.e., aurothioglucose, gold sodium thiomalate, auranofin) have minimal anti-inflammatory activity.
- The primary mechanisms of action may be inhibition of mononuclear phagocyte maturation and function.
 - Gold is sequestered in mononuclear phagocytes within the inflamed synovium.
 - Gold thiomalate reduces migration and phagocytic activity of macrophages in inflammatory exudates, as well as lysosomal enzyme activity.
 - Gold depresses cell-mediated immunity (CMI).

Preparations and Administration

- Aurothioglucose is water-soluble (50% gold), but it is given by intramuscular injection as a sterile suspension in fixed oil; each dose contains 50 mg/mL.
- Water-soluble gold sodium thiomalate (50% gold) is also given by intramuscular injection.
- Auranofin (29% gold) is taken orally for active rheumatoid arthritis.
 - Initial clinical responses (effects) may not be detected until 10-12 weeks of therapy.

- Therapy should be discontinued if, even after 3 additional months, response is still inadequate.
- Auranofin may be somewhat less effective than injectable gold for rheumatoid arthritis, but it is less toxic and better tolerated.

Adverse effects: Treatment with gold is associated with several adverse effects and only 60% continue of patients remain continue on treatment at the end of 2 years. Adverse effects occur in 25%-50% of patients on chrysotherapy.

Adverse effects includes:

- *On skin and mucous membrane:* Dermatitis, pruritus, stomatitis, pharyngitis, glossitis, gastritis, colitis and vaginitis. A gray blue pigmentation on exposed parts of the skin may be seen.
- *Renal toxicity:* Hematuria, glomerulonephritis.
- *Liver:* Hepatitis, cholestatic jaundice
- *Nervous system:* Encephalitis, peripheral neuritis.
- *Blood:* Thrombocytopenia, leukopenia, agranulocytosis, aplastic anemia.
- *Lungs:* Pulmonary fibrosis.
- *CVS:* Postural hypotension.

Contraindications: Kidney, live and skin diseases; pregnancy and blood dyscrasias.

Therapeutic uses

- *Rheumatoid arthritis:* Gold is used in active arthritis that progresses despite on adequate course of NSAIDs, rest and physiotherapy. In most patients gold salts arrest the progression of the disease, improve grip strength, reduce morning stiffness and prevent involvement of unaffected joints.

Gold is also beneficial in:

- Juvenile rheumatoid arthritis
- Psoriatic arthritis
- Palindromic rheumatism
- Pemphigus
- Lupus erythematosus.

d-Penicillamine

Chemistry: It is an analog of the amino acid cysteine and a metabolite of penicillin. It is a chelating agent that chelates copper.

Mechanism of action: Its actions and toxicities are similar to gold but is less effective than gold. They usually suppresses phagocytic activity of macrophages and cell mediated immunity.

Therapeutic uses: Penicillamine in high doses can be effective in patients with refractory rheumatoid arthritis and may delay progression of erosions.

Adverse effects

- Penicillamine is highly toxic and teratogenic, and the most common adverse effects are similar to those of parenteral gold, hence it is not preferred.
- **Adverse effects** include drug fever, skin rashes, proteinuria, leucopenia, thrombocytopenia, aplastic anemia, a variety of autoimmune diseases including lupus erythematosus, thyroiditis and hemolytic anemia. Anorexia, nausea, vomiting, loss of taste perception and alopecia may also be seen.

Chloroquine and hydroxychloroquine: These antimalarial drugs are found to be useful in mild non-erosive rheumatoid arthritis. They induce remission in 50% of patients. They are less effective but are better tolerated than gold.

Mechanism of action: It is not exactly understood but they are known to depress cell-mediated immunity.

Toxicity: Chloroquine and hydroxychloroquine accumulate in the tissues leading to toxicity.

- The most significant side effect is the retinal damage on long-term use (reversible).
- Other adverse effects include myopathy, neuropathy and irritable bowel syndrome.

Dose: Hydroxychloroquine 400mg/day for 4-6 weeks; maintenance dose is 200mg/day.

Sulphasalazine

Chemistry: It is a compound of sulphapyridine and 5-amino salicylic acid.

Pharmacokinetics: In the colon, Sulphasalazine is split by the bacterial action and sulphapyridine gets absorbed.

Action: This has anti-inflammatory actions though the mechanism is not known. It appears to be as effective as penicillamine and may prevent progression of joint damage.

Adverse effects

- It is less toxic. Gastrointestinal disturbances and rashes are common.

Immunosuppressants: Immunosuppressants are cytotoxic drugs and are reserved for patients with seriously crippling disease with reversible lesions after conventional therapy has failed.

- Among the immunosuppressants, **methotrexate** is the best tolerated.

Methotrexate: It produces an antirheumatic effect within 6 weeks of treatment.

Pharmacokinetics: Aspirin and other NSAIDs increase methotrexate's toxicity by slowing its rate of excretion.

Adverse effects

- Methotrexate is immunosuppressive, and opportunistic infections (e.g., herpes zoster, pneumocystis carinii) can occur.
- Lymphomas associated with Epstein-Barr virus infection have occurred but are reversed by discontinuation of therapy.
- At recommended doses, severe toxicity is rare; however, the drug is teratogenic.
- Methotrexate is contraindicated in patients with renal insufficiency or hemodynamic instability.

Leflunomide: It is a prodrug.

- The active metabolite inhibits autoimmune T cell proliferation and production of auto-antibodies by B cells.
- Leflunomide is orally effective, and has a long $t_{1/2}$ of 5-40 days.
- **Adverse effects:** include diarrhea and raised hepatic enzymes.
- **Indications:** Leflunomide is used with methotrexate in rheumatoid arthritis patients not responding to methotrexate alone.

Immunoabsorption Apheresis

- Extra corporeal immuno-adsorption of plasma for the removal of IgG – containing immunocomplexes has been approved for the treatment of moderate to severe rheumatoid arthritis.
- The duration of benefit varies from few months to several years. Adverse effects are mild and tolerable.

TNF blocking agents: Cytokines, particularly tumor necrosis factor (TNF) plays an important role in the process of inflammation. TNF blocking drugs are found to be useful in rheumatoid arthritis.

- TNF α produced by macrophages and activated T cells, acts through TNF receptors to stimulate the release of other cytokines.
- Infliximab is a monoclonal antibody which specifically binds to human TNF.
- When given in combination with methotrexate, it slows the progression of rheumatoid arthritis.
- It is given intravenously.

Adverse effects

- Combination can increase the susceptibility to upper respiratory infections, nausea, headache, cough, sinusitis and skin rashes.
- Antinuclear and anti-DNA antibodies may develop.

Etanercept: It is a recombinant fusion protein that binds to TNF molecules.

- It is found to slow the progression of the disease in rheumatoid arthritis patients. It is given subcutaneously.
- It is also found to be useful in psoriatic and juvenile arthritis. Etanercept is also given with methotrexate and the combination has a higher efficacy.

Adverse effects: Pain, itching and allergic reactions at the site of injection, anti-etanercept antibodies and anti-DNA antibodies have been detected.

Cyclosporine: It is a cyclic peptide derived from fungus used only for patients with severe, progressive disease.

Pharmacokinetics: Oral bioavailability of cyclosporine ranges from 20%-50% and its half-life is about 6 hours. It is metabolized in the liver and most is then excreted in the bile.

Mechanism of action

- Cyclosporine is a highly selective inhibitor of helper T cells. It inhibits the production of interleukin-2 (IL-2) by helper T cells and reduces the production and release of other lymphokines in response to an antigenic stimulus.
- Cyclosporine also binds to lymphoid proteins called cyclophilins and to isomerase enzymes, which aid in the folding of certain proteins.

Therapeutic uses: Cyclosporine is used in combination with prednisone to sustain cardiac, renal, and hepatic transplants. One-year survival is approximately 75%.

Adverse effects

- The major adverse effect is nephrotoxicity, a dose-related phenomenon that occurs in 25%-75% of patients treated with the drug. Both the GFR and renal plasma flow are reduced, but these effects are usually reversible.
- Neurological toxicity, hypertension, and increased incidence of infections are also seen.

Glucocorticoids: Glucocorticoids have anti-inflammatory and immunosuppressant activity. They produce prompt and dramatic relief of symptoms but do not arrest the progress of the disease.

Therapeutic uses: Patients with severe rheumatoid arthritis may benefit from 5-10 mg/day of oral prednisone; patients with vasculitis may require higher doses.

Administration

- Intra-articular corticosteroids are helpful to relieve pain in severely inflamed joints.

- The adverse effects of long-term systemic corticosteroids usually restrict their use for all excluding most severe forms of rheumatoid arthritis.

Capsaicin: It is an alkaloid found in hot peppers, is used topically to relieve arthritic pain.

Diet and Inflammation

- Diet rich in unsaturated fatty acids (such as marine fish), decreases morning stiffness, pain and swelling of the joints.
- Unsaturated fatty acids compete with arachidonic acid for uptake and metabolism and their metabolic products are only weak inflammatory mediators, when compared to the products of arachidonic acid metabolism.
- For people who do not eat fish, eicosapentanoic acid 1-4g/day may be given as tablets. It serves as an adjuvant.

PHARMACOTHERAPY OF GOUT

Definition: Gout is a familial metabolic disorder characterized by hyperuricemia. It is an inherent abnormality of purine metabolism resulting in over production of uric acid. It may be acute or chronic.

- There occurs recurrent episodes of **acute arthritis** due to
 - Deposition of monosodium urate in the joints and cartilages. The joint becomes red, swollen, tender and extremely painful.
 - Uric acid calculi formation (renal stone) and
 - Deposition of urate crystals in subcutaneous tissue: **Tophy**
- **Acute gout:** There is pain in small joints (metatarsophalangeal joints of toes) of sudden, acute origin. It is due to precipitation of urate crystals in joints.
- **Chronic gout:** In between attacks; pain and swelling persists. It is characterized by **tophy** formation (in pinna, eyelids, nose and joints) and renal stone formation. It may progress to permanent deformities and disability.

Uric acid

- It is a major end product of purine metabolism
- It is poorly soluble in water. Especially at lower pH it gets precipitated and deposited in cartilages of joints and ears, subcutaneous tissues, bursa and sometimes in kidneys.
- Mammals contain (uricase) which is absent in human beings.

Uricase → Uric acid → Allantoin (highly water soluble).

Urate crystals



Phagocytosed by Synoviocytes

- Release of interleukin – 1
- Release of prostaglandins
- Release of lysosomal enzymes.
- Increased release of chemotactic mediators.



Migration of Polyleukocytes → Inflammation at joints.

Precipitating factors

- Acute gouty arthritic episodes can be precipitated by excessive alcohol consumption, kidney diseases, and possibly by high-purine diets or external stresses.
- If the gout is a secondary phenomenon unrelated to a genetic defect, the underlying cause of the hyperuricemia must be determined.

Causes of hyperuricemia

- Excessive uric acid synthesis associated with myeloproliferative disorders and malignancies, especially after antineoplastic or radiation therapy, can cause hyperuricemia. Conditions that lead to high rates of cell formation and destruction increase serum levels of purines, because purines are derived from nucleic acids.

Secondary hyperuricemia may occurs in

- lymphomas
- leukemia's and polycythemia
- A primary defect in the rate of purine synthesis can cause hyperuricemia.
- Decreased renal excretion of uric acid can be caused by certain drugs or by a genetic deficiency.
- Drug induced gout (there occurs decreased excretion of uric acid). Drugs are:
 - Thiazide
 - Ethambutol
 - Furosemide
 - Levodopa
 - Pyrezinamide
 - Clofibrate
- Sex-linked uric-aciduria (e.g., in Lesch-Nyhan syndrome) can result from a lack of the enzyme hypoxanthine-guanine phosphoribosyl transferase.
- Strategies in the treatment of gout is either to decrease the biosynthesis of uric acid or enhance the excretion of uric acid.

Classification of Drugs used in Gout

• In acute gout

NSAIDs (Indomethacin, naproxen, piroxicam, etc.)
Colchicine and Corticosteroid

• In chronic gout

Uric acid synthesis inhibitor: Allopurinol
Uricosuric drugs: Probenecid, Sulphinpyrazone.

NSAIDs

- They are the first line of drug for acute attack of gout. They afford symptomatic relief in the treatment of gout.
- They relieve an acute attack in 12-24 hours and are better tolerated than colchicines.
- Indomethacin is the most commonly used agent. Naproxen, piroxicam, phenylbutazone and other newer NSAIDs are also used.
- Aspirin and other salicylates, although they may provide symptomatic relief, actually antagonize the action of the uricosurics, probenecid and sulfinpyrazone. Therefore, the salicylates are contraindicated when probenecid or sulfinpyrazone is being administered.
- NSAIDs acts by inhibiting prostaglandin synthesis. They also inhibit the filtration therefore they ultimately reduces pain, swelling and edema.

Uses :

- a. As a treatment of gout and
- b. As a starter (initiation) or gap filler for chronic gout (allopurinol take 2 –3 weeks for appearance of its effect)

Dose and frequency

- Patient's respond at 25 - 50 mg TID for 5 days (continue for 2 - 3 weeks).
- Ibuprofen : 2400 mg / day - recommendation
- Phenyl butazone : 400 mg followed by 200 mg 6 hourly.
- NSAIDs are not recommended for very long-term use due to their toxicity.

Colchicine

Chemistry: It was first introduced in, 1763. It is an alkaloid obtained from *colchicum autumnale*.

Actions

- It is not an analgesic.
- It is an unique anti-inflammatory agent effective only against gouty arthritis.
- In acute attack, it dramatically relieves pain within a few hours.

Mechanism of action

- Colchicine inhibits the migration of granulocytes into the inflamed area and the release of glycoprotein by them.
- It binds with intracellular protein **tubulin** and then it inhibits
 - Polymerization in microtubule (arrests cell division in metaphase).
 - Leukocytes migration.
 - Phagocytosis.
 - Formation of IL-B₄.
- It increases gut motility by neurogenic stimulation.

Pharmacokinetics

- Colchicine is rapidly absorbed from GIT if taken orally.
- It partially metabolized in the liver and large amounts of it and its metabolites reenter the intestinal tract in the bile and intestinal secretions (i.e. undergoes entero-hepatic circulation).
- Finally excreted via urine/feces.

Adverse effects

- Nausea, vomiting, abdominal pain and diarrhea are the earliest side effects.
- Anemia, leukopenia bone marrow suppression and alopecia (hair loss) may be seen.
- In higher doses hemorrhagic gastroenteritis, nephrotoxicity, CNS depression, muscular paralysis and respiratory failure can occur.
- A fatal dose of colchicines can be as little as 8 mg in 24 hours

Therapeutic indications

- 1 **Acute gout:** Colchicine 1 mg orally initially followed by 0.5 mg every 2-3 hours relieves pain and swelling within 12 hours.
2. **Prophylaxis:** Colchicine may also be used for the prophylaxis of recurrent episodes of gouty arthritis.
3. It is also used for the treatment of sarcoid arthritis and hepatic carcinoma.

Precaution: Colchicine is excreted unchanged by the liver and kidney; therefore, the dosage may have to be reduced if renal or liver disease is present.

Allopurinol (Uric Acid Synthesis Inhibitor)

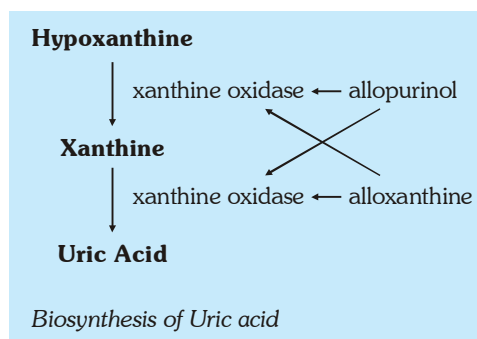
Chemistry: It is an analog of hypoxanthine (a purine) antimetabolite for cancer chemotherapy and inhibits the biosynthesis of uric acid.

Mechanism of action

- Allopurinol, together with its primary metabolite alloxanthine, prevents the terminal steps in uric acid

synthesis by inhibiting the enzyme *xanthine oxidase*, which converts xanthine or hypoxanthine to uric acid.

- Allopurinol acts as a competitive inhibitor, while alloxanthine acts noncompetitively.
- The inhibition of *xanthine oxidase* causes serum levels of the catabolic intermediates xanthine and hypoxanthine to increase.
- Renal clearance of these substances, however, is rapid, and their increased plasma concentrations do not exceed their solubility. Thus, crystallization within joint tissue does not occur as it would with comparable levels of uric acid.

**Pharmacokinetics**

- **Administration.** Allopurinol is administered orally. Starting with a low dose may reduce the probability of precipitating recurrent acute gouty attacks.
- Allopurinol is 80% absorbed orally.
- $t_{1/2}$ of allopurinol is 2–3 hours.
- $t_{1/2}$ of alloxanthine: 24 hours.

Adverse effects

- The most common untoward effects are hypersensitivity reactions, including cutaneous reactions, GIT irritation, headache, nausea and vomiting.
- Acute attacks of gout occur more frequently during initial therapy with allopurinol.
 - This may be due in part to the active dissolution of microcrystalline deposits of sodium urate (tophi) within subcutaneous tissue, resulting in transient periods of hyperuricemia and crystal deposition in joint tissue.

To reduce this complication, simultaneous prophylactic therapy with colchicine is indicated.

Drug interactions

- The anticancer drugs: azathioprine and 6-mercaptopurine are metabolized by xanthine oxidase.
- Therefore, when allopurinol is used concurrently the dose of these anticancer drugs should be reduced.

Therapeutic indication

- Allopurinol is used in chronic gout and secondary hyperuricemia.
- NSAID or a Colchicines should be given during the first few weeks of allopurinol therapy to prevent the acute attacks of gouty arthritis.
- In patients with large tophaceous deposits, both allopurinol and uricosuric drugs can be given.
- On treatment with allopurinol, tophi are gradually resorbed and the formation of renal stones are prevented.
- Frequency and doses: Initial dose is 100mg/day and may be gradually increased to 300mg/day depending on the response.

Uricosuric Drugs

Probenecid: It is an organic acid developed to inhibit the renal tubular secretion of penicillin in order to prolong its action. Probenecid blocks tubular reabsorption of uric acid and thereby promotes its excretion.

Mechanism of action and pharmacological effects

- Probenecid has no analgesic activity.
 - At therapeutic doses, probenecid lowers serum levels of uric acid by inhibiting the proximal tubular reabsorption of uric acid.
 - In low doses, probenecid blocks the tubular secretion of uric acid, while at therapeutic doses probenecid is uricosuric.
 - When approximately 1 g of probenecid is administered daily, urinary excretion of uric acid increases by 50% resulting in a corresponding decrease in serum urate.
 - The metabolic products of probenecid are also uricosuric.
- As a general inhibitor of the tubular secretion of organic acids, probenecid also increases serum levels of other organic acids, such as penicillin.

Pharmacokinetics: Probenecid is rapidly absorbed from the gastrointestinal tract.

Therapeutic uses

- By virtue of its uricosuric effect, probenecid is useful for the treatment of chronic gout.

- By virtue of its effect on organic acid excretion, probenecid is also used to prolong the effects of penicillin.

Administration: Probenecid is administered orally.

- The action of probenecid is blocked by the administration of aspirin.
- Because of its biphasic action, therapy with probenecid should not be initiated during an acute attack of gout. It is started with 500 mg once a day and gradually increased to 1g /day

Adverse effects: Probenecid is well tolerated, the most common adverse effects being gastrointestinal disturbances and hypersensitivity reactions, such as skin rash and drug fever.

Sulfinpyrazone

Chemistry: Sulfinpyrazone is a sulfoxide derivative of phenylbutazone.

Mechanism of action and pharmacological effects

- Sulfinpyrazone inhibits the proximal tubular reabsorption of uric acid. Its hydroxy metabolite is also a potent uricosuric substance.
- Sulfinpyrazone also inhibits prostaglandin synthesis and interferes with a number of platelet functions, including adherence to sub endothelial cells.

Pharmacokinetics: After oral administration, sulfinpyrazone is well absorbed from the gastrointestinal tract and most is excreted unchanged in the urine.

Therapeutic uses

- Sulfinpyrazone is used for the treatment of chronic gout.
- Because of its effects on platelets, it is being used as an antithrombotic agent.

Administration

- Sulfinpyrazone is given orally.
- Administration with meals is recommended. As with probenecid, sulfinpyrazone therapy should not be initiated during an acute gouty attack.

Adverse effects: are similar to those seen with probenecid.



S E C T I O N

12

Chemotherapy

General Consideration

Chemotherapy: It is the treatment of systemic infection or malignancy with the drugs which are having selective toxicity for the infecting organisms/malignant cells with no or minimal effect on the host cells.

- **Chemotherapeutic agents:** These are the substances, which kills or inhibits the invading microorganisms (malignant cells) with no or minimal pharmacodynamic effect in the recipient cells.
- Pasteur was the first to identify that microorganisms could destroy other microorganisms. Paul Ehrlich '**The father of Modern Chemotherapy**' coined the term 'Chemotherapy'.
- Chemotherapeutic substance should be maximum parasitotropic and minimum organotropic effects.

Antibiotics: They are produced by microorganisms such as fungi, bacteria and actinomycetes. They suppress the growth of other microorganisms and may eventually destroy them and are needed in very small amount. Although antibiotics are mainly produced by microorganisms, many are now obtained semi synthetically and some, for example chloramphenicol, can be completely synthesized. So it will be more appropriate to use the term antimicrobial agents (AMAs) for both synthetic as well as naturally obtained drugs that attenuate microorganisms.

- Domagk in 1936 demonstrated that prontosil, a sulfonamide dye is effective in some infections.
- The production of penicillin (A. Fleming) for clinical use in 1941 marked the beginning of the 'golden era' of antibiotics.
- In the last 65 years, several powerful antibiotics and their semi synthetic derivatives have been produced.

Bactericidal agents

- These antimicrobials irreversibly damage and kill the susceptible microorganisms. They act best against multiplying organisms.
- Examples are penicillin, amino glycosides, cephalosporins, isoniazid, etc. Fungicidal is the term used for killing fungus agents.

Bacteriostatic agents

- These antibiotics/antimicrobials do not kill the organisms. They reversibly inhibit the growth and multiplication of susceptible microorganisms, e.g. sulphonamides, tetracyclines, etc.

Classification of Antimicrobial Agents (AMAs) (Fig. 12.1.1)

1. Narrow spectrum drugs

A. Active against gram positive cocci and bacilli:

- Penicillin G
- Penicillinase resistance penicillin
- Macrolids
- Vancomycin and Lincomycin.
- Bacitracin

B. Active against gram negative bacilli:

- Aminoglycosides
- Polymyxins

2. Broad spectrum drugs

- Chloramphenicol
- Tetracyclines
- Broad Spectrum Penicillins: Ampicillins and Carbenicillines
- Cephalosporines
- Trimethoprim and Cotrimoxazole

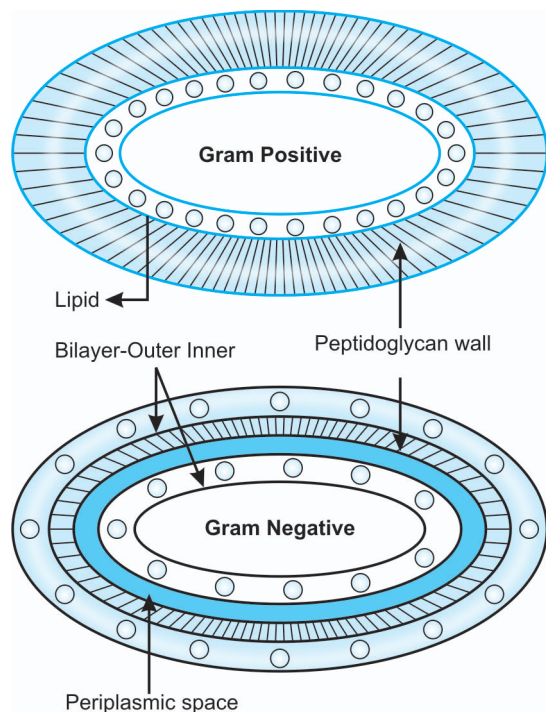


Fig. 12.1.1: Structure of gram (+) and gram (–) bacteria

Classification according to sources of antibiotics:

Fungi	Penicillin Cephalosporine Griseofulvin
Bacteria	Bacitracin and Polymyxin B, etc.
Actinomycetes	Aminoglycosides, Polyenes Tetracyclines, Chloramphenicol, etc.

Classification according to mechanism of action (Fig. 12.1.2)

Based on their mechanism of action, antimicrobials are classified as drugs that:

- 1. Damage cell membrane:** Causing leakage of cell membrane: Polymyxins, Amphotericin B, Nystatin.
- 2. Inhibit cell wall synthesis:** Penicillins, Cephalosporins, Vancomycins, Bacitracin, Cycloserine.
- 3. Inhibit protein synthesis:** Aminoglycosides, Clindamycin.
- 4. Bind to ribosomes:** Chloramphenicol, Tetracyclines, Erythromycin
- 5. Inhibit DNA gyrase:** Fluroquinolones like Ciprofloxacin, Norfloxacin
- 6. Inhibit DNA functions** (DNA dependant RNA polymerase)—Rifampicin

7. Inhibit DNA synthesis: Acyclovir, Zidovudine

8. Interfere with metabolic steps: Sulfonamides, Sulfones, Trimethoprim, Pyrimethamine (antimetabolite action).

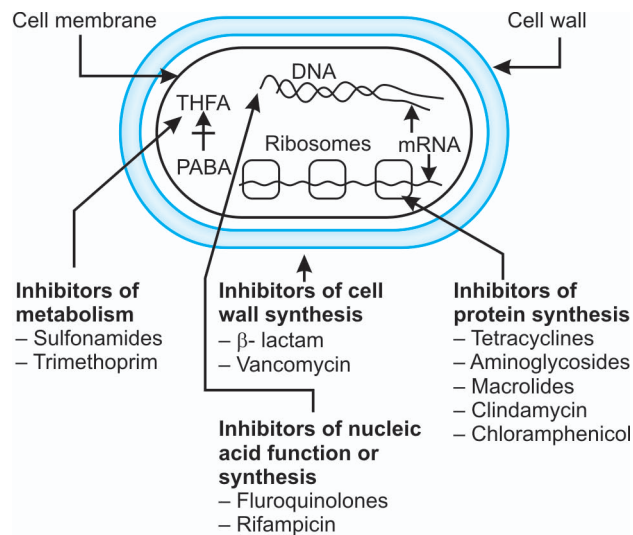


Fig. 12.1.2: Mechanism of action of certain AMA

Factors that influence the successful chemotherapy of an infection are:

- **Site:** The drug should reach the site of infection.
- **Concentration:** It should attain adequate concentration at the site.
- **Host defence:** Active host defences reduce the antibiotic requirement.
- **Sensitivity:** The microorganism should be sensitive to the antimicrobial agent.

Bacterial sensitivity testings

1. KTB: Kirby-Bauer Technique

- Drug impregnated disc were used.
- Clear zone of inhibition is produced

Results – (a) Sensitive, (b) Intermediate sensitive and (c) Resistant

2. MIC: Minimum Inhibitory Concentration

It is the lowest concentration of an antibiotic which prevent visible growth of the bacteria, determined in microwell culture plates using serial dilutions of the antibiotics.

3. MBC: Minimum Bactericidal Concentration.

The MBC of the antibiotics is determined by sub-culturing from tubes with no visible growth.

- Antibiotic levels in tissue fluid (plasma) is very important
- The antimicrobial action depends on the length of time the concentration remains above MIC; division of daily dose has better effect. However the dose

should be so spaced that whenever the surviving organisms restart multiplying, the cidal effect (action) can be exerted upon.

Resistance to Antimicrobial Agents

A state of unresponsiveness or insensitivity or decrease in sensitivity of microorganisms to drug (antimicrobial agent) is called bacterial resistance. It may occur in originally sensitive microorganisms which undergo a genetic change

- The resistance may be
 - a. Natural or
 - b. Acquired

Natural resistance

In natural resistance the organisms have never responded to the anti-microbial agent: may be due to the absence of the particular enzyme or target site affected by the drug, e.g. gram-negative bacilli are not sensitive to Penicillin G. *As alternate drugs are available, this type of resistance is clinically not a problem.*

Acquired resistance

Here, the microbes which were previously sensitive to the anti-microbial agents become resistant to AMA later on. Clinically this causes a problem.

- Bacteria acquire resistance by a change in their DNA. Such DNA changes may occur by: (i) Mutation or (ii) $\otimes \rightarrow$ Transfer of genes.

1. Mutation

- Mutation is the common cause of resistance to antimicrobial agents. It is a stable and heritable genetic change. It occurs spontaneously and randomly among microorganisms.
- In any population of bacteria, a few resistant mutants may be present. When the sensitive organisms are destroyed by the antibiotic, the resistant mutants freely multiply.
- It (mutation) may be a **single step mutation** resulting in high degree of resistance as seen in case of streptomycin, and rifampicin. In other cases, it may be a **multiple step mutation** in which resistant mutants may emerge by a slow stepwise process, e.g. in case of penicillin.

2. Transfer of genetic material

- Many bacteria contain extra chromosomal genetic material called **plasmids** in the cytoplasm. These carry genes coding for resistance (called R-factors).
- These R-factors are transferred to other bacteria and spread resistance: *This may take place by:*
 1. **Conjugation:** It is the important mode of spread of resistance. The R-factor (extra chromosomal genetic material), is transferred from one bacterium

to another by direct contact through a sex pilus or bridge (connecting tube) and the process is known as conjugation.

2. **Transduction:** Plasmid DNA is transferred through bacteriophage, i.e. viruses which infect bacteria.
3. **Transformation:** In this case, a resistant bacterium may release the resistance carrying DNA into the medium which may be imbibed by another sensitive organism (bacteria). Due to this, the recipient bacteria becomes unresponsive to drug.

Mechanism of Resistance to Antimicrobial Drugs

- **Changing membrane permeability (Biochemical Mechanisms):** Both Gram (+ve) and Gram (–ve) bacteria may develop resistance to tetracycline, amino glycosides, beta-lactamase, chloramphenicol and polymyxins due to biochemical alteration of their envelope. Due to this, accumulation of drug or **intracellular drug level** in the bacteria is decreased.
- **Increase destruction (degradation) of the drug:** The antibiotics can be inactivated by enzymes synthesized by a large number of organisms. Classical examples are:
 - Beta-lactum antibiotics are inactivated by beta-lactamases which are produced by staphylococci and enteric Gram (–ve) rods.
 - Amino glycosides are inactivated by several enzymes which are produced by both Gram (+ve) and Gram (–ve) organisms.
 - Chloramphenicol is inactivated by chloramphenicol acetyltransferase, produced by resistant strains of Gram (+ve) and Gram (–ve) organisms (See Fig. 12.1.1).
- **Altered structural target for the drug:** The binding site may be altered, e.g. binding sites for Aminoglycosides, on the ribosome's may be altered due to mutation.
- **Altered metabolic pathway:** Staphylococci and many other bacteria may show resistance to sulphonamides and trimethoprim by developing alternative metabolic pathways.
- **Efflux pump:** Some gram (–ve) bacteria can develop an enzyme, which can pump out terramycin from their body, so that the antibiotic can not be concentrated in these bacterial bodies.

Cross resistance

- It is the resistance seen among chemically related antimicrobial agents.
- When a microorganism develops resistance to one drug (AMA), it is also resistant to other drugs (AMA) of the same group having the same mechanism of action, even

when not exposed to it, e.g. resistance to one tetracycline means resistance to all other tetracyclines. Other examples includes sulphonamides, beta-lactam antibiotics, amino glycosides, etc.

Multiple antibiotics resistance

Sometime a particular strain of bacteria may be resistant to many antibiotics. Such bacterial strains are called “multi-drug resistant” strains.

Test for resistance

Three methods are described for testing the specimen for resistance

- Disk diffusion (Kirby-Bauer technique).
- MIC
- Well method.

Prevention of resistance to antimicrobials

Drug resistance can be avoided to some extent by taking following measures:

- Antibiotics should be used only after confirmed diagnosis and when necessary.
- Prefer narrow spectrum antibiotics as compared to broad spectrum as far as possible.
- Selection of the appropriate antibiotic is absolutely important.
- Never treat the patient half heartedly; correct dose and duration of treatment should be followed.
- Combination of drugs should be used as in tuberculosis to delay the development of resistance.

COMBINATION OF ANTIMICROBIALS

The simultaneous use of two or more antimicrobial agents is some times justified. Combinations should be judiciously chosen keeping in mind their effect on the microorganisms as well as the host. The combination serves one of the following purposes.

1. In the treatment of mixed infections

- Genitourinary infections, Intra-abdominal infections, brain abscesses* are often mixed infections. Aerobic and anaerobic organisms may be involved.
- Combination of two or more anti-microbial can be used depending on the culture and sensitivity report.

2. To obtain synergism

Combination of antibiotics to attain synergism is recommended in:

- Amoxicillin and clavulanic acid to enhance antibacterial spectrum
- Bacterial endocarditis*: Penicillin + streptomycin/gentamicin is synergistic.
- Pseudomonas infections*: Carbenicillin + gentamicin

- Pneumocystic carini pneumonia*: Trimethoprim + sulfamethoxazole
- Amoxicillin + clavulanic acid—b-lactamase producing organisms like *H. influenzae*.
- Tuberculosis*: INH + rifampicin.
- Amphotericin B and rifampin in antifungal infection

3. In treatment of severe infections

Severe infections of unknown etiology as in septic shock with urinary tract infection, combination can be used:

- Drugs covering both gram-positive and gram-negative pathogens may be used initially till the culture report is available, e.g. penicillin + aminoglycoside; cephalosporin + aminoglycoside.
- If anaerobes are likely to be present, **metronidazole** may be added. Samples for culture should however be taken before starting the antibiotics.

4. To reduce the adverse effects

- The doses needed may be lower when a combination is used.
- This may reduce the incidence and severity of adverse effects, e.g. Amphotericin B + flucytosine in cryptococcal meningitis.

5. To prevent emergence of resistance

- In the treatment of *tuberculosis and leprosy*, combinations of drugs are used to prevent development of resistance.

Disadvantages of antimicrobial combination

- Increased cost of therapy.
- Toxicity: In each agent—especially if toxicity is overlapping—may get added up. Toxicity of one drug may be enhanced by another, e.g. many antitubercular drugs are hepatotoxic.
- Vancomycin + aminoglycoside → more severe renal toxicity
- Selection of resistant strains: the few resistant mutants that remain may multiply unchecked.
- Emergence of organisms resistant to multiple drugs.

SUPERINFECTIONS (OPPORTUNISTIC INFECTION)

Definition: Superinfection/supra-infection is the appearance of a infection resulting from the use of antimicrobials. Antimicrobial therapy, especially with broad/extended spectrum antibiotics, may lead to superinfection (over growth) with *Proteus*, resistant staphylococci, *Pseudomonas*, *clostridium difficile* or *candida* due to the removal of

natural antibiosis of nonpathogenic organisms against pathogenic ones in the intestinal, respiratory and genitourinary tracts

- Antibacterial alter the normal microbial flora of the intestinal, respiratory and genitourinary tracts.
- The normal flora contributes to host defense mechanisms as follows—they inhibit colonization of pathogenic organisms by producing antibacterial substances called bacteriocins and by competing for nutrients.
- When the normal flora is destroyed by antibacterial agents, there can be dangerous infections due to various organisms especially the normal commensals.
- Opportunistic infections are more common when the patient's immune systems are compromised by diseases or drugs, e.g. during cancer chemotherapy and prolonged use of corticosteroids and patients of AIDS or even diabetes.
- The broader the antibacterial spectrum of a drug, the more is the chances of super-infection, as the alteration of the normal flora is greater. Common microorganisms causing super infections are given in the box below.

Misuse of antibiotics

- Antibiotics are most overused or misused drugs.
- Faulty practices of antibiotics like the use of antibacterial agents in viral infections which are self-limiting, using too low doses or unnecessary prolonged treatment, using antibiotics in all fever cases: are all irrational and can do more harm than any benefit.

SELECTION OF AN ANTIBACTERIAL AGENT

An ideal chemotherapeutic agent should be selectively toxic to the organism without producing any harmful effects to the host. So the physician should select a proper antimicrobial agent based on various factors like:

- The patient factors,
- The microbe factors,
- The properties of the drug and
- The clinical assessment.

- Age of the patient, host defense status, renal and hepatic functions should be considered.
- Whenever possible, bacteriological culture should guide the drug selection. Narrow spectrum antibiotics are always better than broad spectrum antibiotics, except certain conditions.
- When bacteriological examination is not possible, empirical therapy (broad spectrum antibiotics) should be started to cover all the likely organisms.
- Drug toxicity and cost should be borne in mind. With proper clinical judgment considering the above factors, most infections can be successfully treated.

Antibiotics are used in two ways:

1. Empirical therapy

The antibiotic must cover all the likely pathogens. A combination of drugs or a broad spectrum agent may be used. This therapy should be employed only in some specific situations like mixed infections.

2. Definitive therapy

When the organism is identified, specific antibacterial agents should be given.

Chemoprophylaxis

Chemoprophylaxis is the use of antimicrobial agents to prevent infection. This is recommended in the following situations:

1. To protect healthy persons

- Penicillin G is given for prevention of gonorrhea or syphilis in patients after contact with infected personnel.
- For preventing meningococcal infection in all healthy children during an epidemic: *rifampicin* or *sulfonamides* may be used.

2. To prevent infection in high risk patients

- In neutropenic patients—penicillin or fluoroquinolones or cotrimoxazole may reduce the incidence of bacterial infection.

Microorganisms	Manifestations	Treatment
Candida albicans	Oral thrush, diarrhea, vaginitis	Clotrimazole
Staphylococci	Enteritis	Cloxacillin
Clostridium difficile	Pseudomembranous Enterocolitis	Metronidazole, Vancomycin
E. coli		Norfloxacin
Pseudomonas	UTI	Carbenicillin

- In patients with valvular heart diseases even minor procedure like dental extraction, tonsillectomy or endoscopies may result in bacterial endocarditis (damage to mucosa results in bacteraemia). *Penicillin is used for prophylaxis.*
- 3. Surgical prophylaxis:** Certain guidelines are to be followed:
- Adequate antibacterial activity should be present during surgery. Hence the drug should be started before surgery.
 - The drug should not be continued beyond 24 hours (risk of resistance).
 - The drug should be effective against all organisms that are likely to contaminate the wound.

Sulfonamide and Cotrimoxazole

SULFONAMIDES

- Sulfonamides were the first chemotherapeutic agents.
- Domagk in 1937 first discovered that Prontosil (a dye) contain Sulfanilamide, which is effective against many gram (+) and gram (–) organism.
- They were employed systematically for the prevention and cure of bacterial infection in man. But, with the development of safe and effective antibiotics and emergence of sulphonamide resistant strains, their importance as chemotherapeutic agents has decreased.
- Sulphonamides are derivatives of p-amino-benzoic acid (PABA). A free amino group in the para position is essential for its antibacterial activity.

Classification

1. Short-acting—Sulfisoxazole, Sulfadiazine
2. Intermediate-acting—Sulfamethoxazole
3. Long-acting—Sulfamethoxypyridazine, Sulfadoxine
4. For special purpose (Poorly absorbed)—Sulfasalazine
5. For special purpose (Topical)—Sulfacetamide, Mefenide, Silver sulfadiazine

Antibacterial spectrum

- Sulphonamides are bacteriostatic agents.
- Sulfonamides inhibit gram-positive and some gram-negative bacteria, nocardia, chlamydiae and some protozoa.
- It may attain bactericidal concentration in urine.

Mechanism of action

- Bacteria synthesize their own folic acid from p-amino benzoic acid (PABA) with the help of the enzyme

dihydrofolate synthetase. (5000 times more active against bacterial DHFRse than mammalian)

- Sulfonamides are structurally similar to PABA and therefore they competitively inhibit the enzyme *dihydrofolate synthetase* and block the utilization of PABA. Due to this, they prevent the synthesis of folic acid which is essential for bacterial growth. This results in folic acid deficiency and damage to the bacterial cell.
- Human beings do not synthesize folic acid. They obtain it through their diet. Hence, sulfonamides selectively inhibit microbial growth only.
- Their antibacterial activity can be prevented or reduced due to presence of pus, tissue fluids and drugs that contain PABA.

Resistance

- Bacterial resistance to sulfonamides has emerged due to widespread indiscriminate use, especially in cocci and gram-negative bacilli.
- Resistance occurs either due to mutation of *dihydrofolate synthetase* resulting in over production of PABA, or by using alternate metabolic pathway for folic acid synthesis by bacteria or by pertaining low permeability to sulfonamides.

Pharmacokinetics

- Sulfonamides are well-absorbed, extensively bound to plasma proteins and are widely distributed throughout all the tissues of the body. They can cross the placental barrier and reach the fetal circulation.
- Sulfadiazine and sulfisoxazole are effective in meningeal infections because they can reach in adequate concentrations in cerebrospinal fluid.

PABA + Pteridine residue $\longrightarrow$ dihydropteroic acid + Glutamic acid $\longrightarrow$ dihydrofolic acid

Sulfonamide + Pteridine residue $\longrightarrow$ Pseudo dihydropteroic acid + Glutamic acid $\rightarrow$ pseudo dihydrofolic acid
(Toxic to bacteria)

- They are metabolized in liver and excreted in urine in free (active) and acetylated (inactive) forms.

Adverse effects

1. Headache, anorexia, nausea, vomiting and abdominal pain.
2. Burning sensation during urination, hematuria, albuminuria and **crystalluria** due to precipitation of the drug in acidic urine. This can be avoided by intake of large volumes of fluids and by alkalinizing the urine.
3. Allergic and hypersensitivity reactions like rashes, fever, photosensitivity, steven-johnsons syndrome, agranulocytosis, thrombocytopenia and vasculitis and rarely exfoliative dermatitis have been reported.
4. Hemolytic anemia: In presence of deficiency of glucose-6-phosphate dehydrogenase (G-6-PD), sulphonamides may lead to hemolytic anemia.
5. Kernicterus: Sulfonamides displace bilirubin from binding sites which crosses BBB and may cause kernicterus in the newborn. Hence contraindicated in pregnancy and in infants.

Drug interactions may occur due to plasma protein binding property of sulfonamides.

It inhibits the metabolism of phenytoin and warfarin, therefore increase their action.

Preparations and doses

1. **Rapidly absorbed and rapidly eliminated sulfonamides:** Sulfadiazine, sulfisoxazole, sulfamethoxazole are used in doses of 2-4 gm followed by 1 gm 6 hours orally.
2. **Well absorbed but poorly excreted sulfonamides:** Sulfamethoxy pyridazine, sulfamoxole, sulfaphenazole are given in doses of 1 gm (initially) followed by 0.5 gm daily orally. Sulfamethoxine is given in single dose of 2 gm every 7th day.
3. **Poorly absorbed sulfonamides:** P-Sulfathiazole, and succinyl sulfathiazole are used for intestinal disinfection in doses of 10-20 gm daily in divided doses. Sulfasalazine is another sulfonamide which is employed in intestinal disorders in doses of 2-8 gm per day (ulcerative colitis and regional enteritis).
4. **Sulfonamides for topical use:**
 - **Sulfacetamide:** Its sodium salt is extensively used in the management of ophthalmic infections. Ophthalmic solutions of 10, 20 and 30% concentrations and ointment (10%) are used. Usual dose is 1-2 drops three to four times a day.
 - **Silver Sulfadiazine:** It is used topically in concentration of 1% to reduce the microbial infections of wounds from burns.

- **Mefenide:** It is used in concentrations of 2-5% cream locally for reducing the infection of burn wound.

Therapeutic indications

1. **Urinary tract infections:** Sulfonamides may be used in areas where resistance is not high.
2. **Nocardiosis:** High doses of sulfonamides can be used.
3. **Toxoplasmosis:** Sulfonamides with pyrimethamine is the treatment of choice.
4. **Trachoma and conjunctivitis:** Tetracyclines are the drug of choice, sulfonamides are used as alternative.
5. **Lymphogranuloma venereum and chancroid:** Sulfonamides are used as alternative to tetracyclines.
6. **Malaria:** Sulfadoxine is used with pyrimethamine in chloroquine resistant malaria.
7. **Ulcerative colitis:** Sulfasalazine is useful in ulcerative colitis and rheumatoid arthritis.
8. **Prophylactic use:** In patients allergic to penicillins, sulfonamides may be used for prophylaxis of streptococcal pharyngitis and in rheumatic fever.
9. **Topical:** Sulfacetamide eye drops are used in bacterial conjunctivitis; mafenide and silver sulfadiazine are used in **burns** to prevent infection.

Because of the development of resistance and availability of better antimicrobials, sulfonamides are not commonly used now except in a few cases.

TRIMETHOPRIM

- It is pyrimidine derivative. It inhibits the enzyme dihydrofolate reductase which catalyses the conversion of dihydrofolic acid to tetrahydrofolic acid, essential for bacterial growth.
- It is bacteriostatic and effective against most common bacterial pathogens. Resistance to trimethoprim develops due to mutation of bacterial dihydrofolate reductase.
- It is commonly used in combination with selected sulphonamides. Its pharmacokinetics is similar to that of sulfonamides. However, it is highly concentrated in prostatic and vaginal fluids due to its relatively acidic nature.
- Nausea, vomiting and skin rashes are common adverse reactions. Rarely, megaloblastic anemia occurs which can be prevented by folic acid.
- Specifically used in treatment of prostatitis and UTI.

COTRIMOXAZOLE

- The combination of *trimethoprim* (80 mg) and *sulfamethoxazole* (400 mg) is cotrimoxazole.

- It is introduced in 1969. Trimethoprim (di-amino-pyridine) is effective against several gram-positive and gram-negative organisms.
- Both the drugs are well absorbed from gastrointestinal tract. About 75% of trimethoprim and 65% of sulfamethoxazole are bound to plasma proteins.
- Up to 60% of trimethoprim and 25-50% of sulfamethoxazole are excreted in the urine in 24 hours.
- There are many advantages of this combination. The combination has bactericidal effect due to sequential block of bacterial tetrahydrofolate synthesis.
- Antimicrobial spectrum is wider (active against salmonella) and toxicity is reduced doses in the combination. Chances of drug resistance are reduced due to dual mode of action (Fig. 12.2.1).

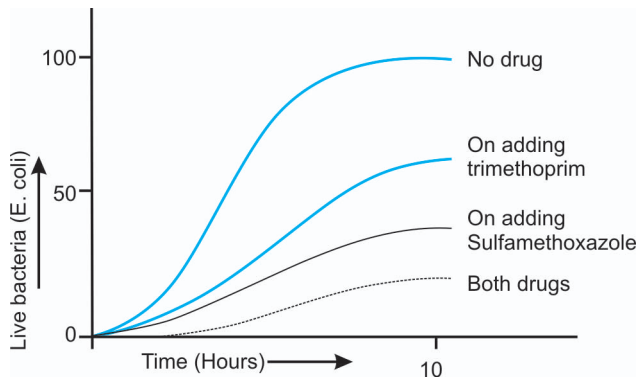


Fig. 12.2.1: Spectrum of activity

Spectrum of activity

- Cotrimoxazole is effective against several *gram-positive* and *gram-negative* organisms like *Staph. aureus*, *Streptococci*, *Meningococci*, *C. diphtheriae*, *E.coli*, *Proteus*, *H. influenzae*, *Salmonella* and *Shigella*.

Mechanism of action (Fig. 12.2.2)

- Sulfonamides inhibit the conversion of PABA to dihydrofolic acid (DHF) and trimethoprim inhibits dihydrofolate reductase (DHFR) and thus prevents the reduction of DHF to tetrahydro-folic acid (THF).
- The two drugs thus block sequential steps in folic acid synthesis and the combination is bactericidal.
- The ratio of 'trimethoprim: sulfamethoxazole' used is 1:5 to attain the high plasma concentration of (1: 20).

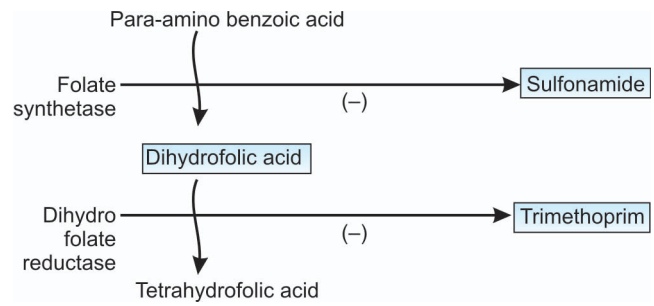


Fig. 12.2.2: Mechanism of action

- Among sulfonamides, sulfamethoxazole is chosen since its pharmacokinetic properties closely match with that of trimethoprim.

Resistance

- Development of resistance to the combination is slower when compared to either drug given alone.
- Bacteria may acquire resistance by mutation or by acquisition of a plasmid coding for an altered DHFR.

Adverse effects

- Nausea, vomiting, headache, glossitis, stomatitis and allergic skin rashes are relatively common.
- In patients with **folate deficiency**, cotrimoxazole may precipitate **megaloblastic anemia**.
- Patients with renal disease may develop uremia.
- Hematological reactions like blood dyscrasis, anemia and granulocytopenia are rare.
- AIDs patients are more prone to adverse effects to cotrimoxazole.

Contraindication

- Pregnancy
- Uremia
- With diuretics
- Bone marrow depression.

Preparations

Trimethoprim	Sulfamethoxazole (SEPTRAN, CIPLIN)
80 mg	400 mg
160 mg	800 mg—double strength (DS)

Therapeutic indications

1. **Urinary tract infection:** Uncomplicated acute UTI is treated for 7-10 days (DS, twice a day) with cotrimoxazole.

2. **Chronic and recurrent UTI**—small doses are given for prophylaxis.
3. **Respiratory tract infections:** Upper and lower respiratory infections including bronchitis, sinusitis and otitis media respond.
4. **Chancroid:** Cotrimoxazole (DS, BD for 7 days) is the drug of choice.
5. **Bacterial prostatitis:** Trimethoprim attains high concentration in prostatic fluid.
6. **Bacterial gastroenteritis:** Due to shigella and *E. coli* respond to cotrimoxazole.
7. **Typhoid:** Cotrimoxazole is used as an alternative to fluoroquinolones.
8. **Pneumocystis carinii infection:** Cotrimoxazole is used for prophylaxis and treatment (high doses) of *Pneumocystis carinii* pneumonia in neutropenic and AIDS patients. It also protects against infection with other gram-negative bacteria.

Beta-lactam Antibiotics

BETA-LACTAM ANTIBIOTICS

- The antibiotics which are having a β -lactam ring in their structure are β -lactams.
- *Penicillins, cephalosporins, carbapenems and monobactams* are β -lactams. Penicillins are one of the most important groups of antibiotics (β -lactams)

PENICILLINS

- **Sir Alexander Fleming** in 1928 discovered Penicillin from the fungus *Penicillium chrysogenum* (penicillium mould).
- Although it was discovered by Alexander Fleming, it was first used as antibacterial therapy by Chain and Flourey in 1941.
- The basic nucleus of penicillin is 6-aminopenicillanic acid. Penicillin has:
 - A thiazolidine ring
 - A β -lactam ring and
 - A side chain

Mechanism of action (Fig. 12.3.1)

- The penicillin is bactericidal.
- The prokaryotic cell of the bacteria contains cell wall which consists of "Peptidoglycans".
- The internal osmotic pressure inside gram positive bacteria is 20 atmospheres. While in that of gram negative bacteria is approximately 5 atmospheres. The rigid cell wall of the bacteria (due to Peptidoglycans) protects it from lyses.
- **Peptidoglycan:** A complex polymer is an important component of the cell wall. β -lactam antibiotics inhibit the synthesis of this peptidoglycan by inhibiting the final step in transpeptidation, resulting in the formation of cell wall deficient bacteria. These undergo auto burst and lyses due to excessive internal osmotic pressure.

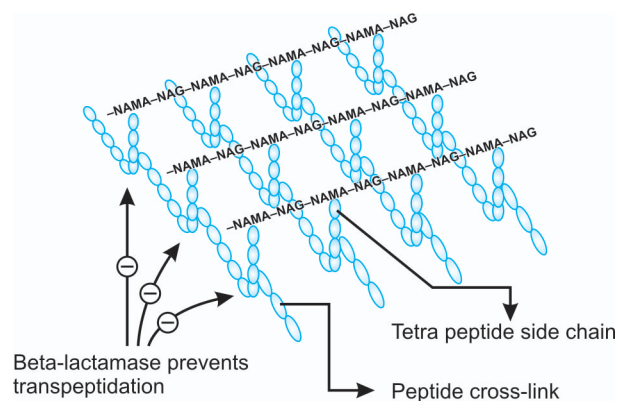


Fig. 12.3.1: Mechanism of action of β -lactam antibiotics

Classification of Penicillins

- **Natural Penicillins:** Benzyl penicillin and Benzathin penicillin.
- **Semisynthetic**
 - 1. Acid resistant penicillin**
Penicillin – V (phenoxy-methyl penicillin)
 - 2. Penicillinase resistant penicillins**
Cloxacillin, Methicillin, Oxacillin, Nafcillin, Temocillin, Flucloxacillin
 - 3. Broad spectrum penicillins**
Aminopenicillins: Ampicillin, Bacampicillin, Amoxicillin, Hefacillin, Pivampicillin.
 - 4. Extended spectrum penicillins**
 - Carboxypenicillins: Carbenicillin, Carbenicillin-indanyl, Ticarcillin
 - Ureidopenicillins: Mezlocillin, Piperacillin.
 - Mecillinam: Amdinocillin
 - 5. Beta-lactamase inhibitor**
 - Clavulanic acid
 - Sulbactam, Tazobactam.

NATURAL PENICILLINS (Table 12.3.1)**Benzyl Penicillin (Penicillin G)****Pharmacokinetics**

- **Benzyl Penicillin** is acid labile, i.e. destroyed (at acidic pH) by gastric juice; food interferes with its absorption: therefore it is advised to be administered 2 hours after food.
- It has a short $t_{1/2}$ period of 30 minutes, but in infants, it is longer. It does not readily cross the blood brain barrier, but due to inflammation, it can penetrate in the CSF therefore can be used in the treatment of meningitis.
- It is secreted and excreted by the kidneys.
- Probenecid blocks the renal tubular secretion of penicillin and thereby prolongs duration of action of penicillin.

Spectrum of activity

- It has a narrow antibacterial spectrum.
- It is effective against gram-positive cocci and bacilli and a few gram-negative cocci.
- Thus *Pneumococci*, *Streptococci*, *Gonococci*, *Meningococci*, *B. Anthracis*, *C. Diphtheriae*, *Clostridia*, *Listeria* and *Spirochetes* are highly sensitive to it.

Resistance

- Many organisms/bacteria synthesize penicillinase, an enzyme, which is a beta-lactamase: which breaks the beta-lactam ring and inactivates penicillin.
- Altered target proteins on the bacterial cell which reduces affinity for penicillin also lead to resistance.

Preparations and dose

- PnG is mainly given parenterally, though orally active form (potassium PnG) is available.
- Oral penicillin is used principally in minor infections. Since it is short-acting, longer-acting repository forms like procaine penicillin and benzathine penicillin—which are made available.
- On giving deep IM, they release penicillin slowly from the site
- Procaine penicillin is given 12 - 24 hourly while a single injection of benzathine penicillin is effective for 3-4 weeks.
- 1 IU of penicillin = 0.6 microgram of Standard Penicillin G
- 1 mega-unit = 0.6 gm of PnG
- Therapeutic index of penicillin is very high that's why it is safer.
- Hypersensitivity due to PnG is the most common cause of **drug allergy**.

- Though all forms of penicillins can cause allergy, anaphylaxis is more common following parenteral than oral preparations. The highest incidence is with procaine penicillin where allergy is most often due to the procaine component. There is cross-sensitivity among different penicillins. Skin rashes, urticaria, fever, bronchospasm, serum sickness and rarely exfoliative dermatitis and anaphylaxis.
- Topical penicillins are highly sensitizing and their use is banned now a days.

Adverse effects

History of allergy to penicillins should be taken before prescribing; incidence is higher among individuals. A scratch test or intradermal sensitivity test with 2-10 units should be done. Even if this is negative, it does not completely rule out allergy. Penicillin should be given cautiously and a syringe loaded with **[adrenaline, antihistaminics and steroid]** should be kept ready to treat anaphylaxis should be kept ready.

Other adverse effects

- Thrombophlebitis and local pain at the site of injection, on IV injection.
- CNS: Large doses of PnG may produce muscle twitching, confusion, convulsions and coma.
- **JH reaction (Jarisch-Herxheimer reaction):** When penicillin is injected in a patient with syphilis, there is sudden destruction of spirochetes and release of its lytic products. This triggers a reaction with fever, myalgia, shivering, exacerbation of syphilitic lesions and vascular collapse.
- Suprainfections are rare due to its narrow spectrum of activity.

Therapeutic indications of penicillin

Penicillin G is the antibiotic of choice for several infections unless the patient is allergic to it.

- 1. Pneumococcal infections:** PnG is the drug of choice for infections due to penicillin-sensitive pneumococci, like pneumonia, meningitis and osteomyelitis.
- 2. Streptococcal infections:** Pharyngitis, sinusitis, pneumonia, meningitis and endocarditis are all treated with penicillin.
- 3. Meningococcal infections:** PnG is the drug of choice for all meningococcal infections.
- 4. Staphylococcal infections:** Since most staphylococci produce penicillinase, a penicillinase resistant penicillin should be used.
- 5. Syphilis:** It is treated with procaine penicillin for 10 days or with benzathine penicillin.

6. **Diphtheria:** Antitoxin is the only effective treatment. PnG eliminates carrier state.
7. **Anaerobic infections:** Pulmonary, periodontal and brain abscesses due to anaerobes respond to PnG.
8. **Actinomycosis:** PnG is the drug of choice
9. **Tetanus and Gas gangrene:** Antitoxin is the treatment for tetanus—but PnG has adjuvant value.
10. **Other infections:** PnG is the agent of choice for infections like anthrax, trench mouth and listeria infections.

Prophylactic uses

- **Rheumatic fever:** Benzathine penicillin 1.2 MU every month prevents colonization by streptococci and thereby decreases the recurrences of rheumatic fever. It is to be continued for several years.
- **Gonorrhea and syphilis:** Sexual contacts are effectively protected against these diseases when treated with penicillin within 12 hours of exposure.
- **Heart diseases:** Bacterial endocarditis seen following dental extractions, endoscopies and other minor surgical procedures due to bacteremia should be **given penicillin prophylaxis**.

SEMISYNTHETIC PENICILLINS (Table 12.3.1)

Acid Resistant Penicillins

- Penicillin V (Phenoxymethyl penicillin) is acid stable and can be given orally.
- It is used only in mild streptococcal pharyngitis, sinusitis and trench mouth.
- Dose: 250-500 mg 6 hourly.

Penicillinase Resistant Penicillins

- They are resistant to hydrolysis by penicillinase produced by bacteria.
- However, against other microorganisms, they are less effective than PnG.
- Methicillin is destroyed by gastric juice, hence given parenterally. Cloxacillin is given orally.

Uses

- Penicillinase resistant penicillins are the drugs of choice for infections with Preparation, doses and route of administration of some cephalosporins.
- Penicillinase producing staphylococci. Methicillin resistant strains have now emerged and are treated with vancomycin.

EXTENDED SPECTRUM PENICILLINS

Aminopenicillins

- These agents cover a wider antibacterial spectrum including many gram-negative bacilli.
- They are orally effective but are sensitive to beta-lactamases.

Antibacterial spectrum

- Both gram-positive and gram-negative organisms including *Streptococci*, *Meningococci*, *Pneumococci*, *H. Influenza*, *E. Coli*, *Proteus*, *Salmonella*, *Shigella* and *Klebsiella* are sensitive. Many strains are now resistant.

Ampicillin

- It is well-absorbed through GIT; food interferes with absorption. It is excreted mainly through kidneys.

Adverse effects: Diarrhea due to irritation of the gut by the unabsorbed drug is the most common adverse effect with ampicillin. Skin rashes are also fairly frequent.

Therapeutic indications

1. **Respiratory Tract Infections:** Bronchitis, sinusitis and otitis media respond to ampicillin.
2. **Urinary Tract infection:** Though ampicillin was the drug of choice earlier, many organisms have now become resistant.
3. **Meningitis:** Ampicillin is given with a cephalosporins.
4. **Typhoid:** Ampicillin is an alternative to ciprofloxacin.
5. **Septicaemia due to gram-negative organisms:** Ampicillin may be used with an aminoglycoside.

Bacampicillin

- It is an ester of ampicillin. It is a prodrug that is better absorbed (hence diarrhea is less common) and longer-acting than ampicillin.

Amoxicillin

1. It differs from ampicillin in the following points: Amoxicillin is preferred over ampicillin by many reasons.
 - Amoxicillin is better absorbed orally
 - Food does not interfere with its absorption
 - Diarrhea is rare
 - Given thrice daily

ANTIPSEUDOMONAL PENICILLINS

Carboxypenicillins

- **Carbenicillin:** It is neither penicillinase resistance nor acid resistance but has extended spectrum of activity.

Table 12.3.1: Preparations, dose and route of administration of penicillins

Drug	Dose	Route	Trade name
NATURAL PENICILLINS			
Sodium penicillin G (Crystalline penicillin)	0.5-5 MU 4-6 hr	IM/IV	CRYSTAPEN
Procaine penicillin G	0.5-1 MU 12-24 hr	IM	PROCAINE PENICILLING
Benzathine penicillin G	1.2-2.4 MU every 3-4 weeks	Deep IM	PENIDURELA
SEMISYNTHETIC PENICILLINS			
Penicillin	250-500 mg QD	Oral	CRYSTAPEN-V
Cloxacillin	250-500 mg QD	Oral	KLOX
Dicloxacillin	250-500 mg QD	Oral	BIOCLOX
Nafcillin	1-2 gm 4-6 hr	IV	UNIPEN
Ampicillin	250 mg or 1gm QD	Oral	AMPILLIN
		IM/IV	ROSCILLIN
Ampicillin + Sulbactam	1 gm Ampicillin + 0.5 gm sulb 6-8 hr	IV	SULBACIN
Amoxicillin	250-500 mg TID	Oral	NOVAMOX SYNAMOX
Amoxicillin + Clavulanic acid	250 mg Amox + 125 mg Clav TID	Oral	AUGMENTIN
Piperacillin	3-4 gm 4-6 hr	IV	PIPRAPEN
Ticarcillin	3 gm 4-6 hr	IV	TICAR

It is effective even against *Pseudomonas aeruginosa* and *Proteus* infections.

- It is given parenterally while carbenicillin indanyl is effective orally.
- Both are susceptible to penicillinase.

Adverse effects

- Carbenicillin is used as a sodium salt and in higher doses this excess sodium may cause edema and CCF;
- It may also cause bleeding due to abnormal platelet aggregation.

Ureidopenicillins

They are effective against *Pseudomonas* and *Klebsiella* infections.

Beta-lactamase inhibitors

- β -lactamases are enzymes produced by bacteria that open up or break the β -lactam ring and inactivate the β -lactam antibiotics.

- β -lactamase inhibitors bind to and inactivate β -lactamases preventing the destruction of the β -lactam antibiotics. **Examples are clavulanic acid and sulbactam.**

- **Clavulanic acid** inhibits β -lactamases and is combined with amoxicillin for both oral and parenteral administration.
- It extends the antibacterial spectrum of amoxicillin. The combination is used for mixed nosocomial infections.
- Sulbactam is combined with ampicillin. It is given parenterally for mixed pelvic and other infections.

CEPHALOSPORINS (Table 12.3.2)

- Cephalosporin acrimonies mould produces cephalosporins. They are semisynthetic antibiotics with a β -lactam ring related to penicillin.
- The basic nucleus of cephalosporins is 7-aminocephalosporanic acid. Antibacterial activity of cephalosporin is similar to broad-spectrum penicillin.

Table 12.3.2: Cephalosporins

Generation	Parenteral	Oral
First	Cefazolin	Cephalexin
	Cephalothin	Cephadrine
		Cefadroxil
Second	Cefuroxime	Cefachlor
	Cefamandole	Cefuroxime axetil
Third	Cefotaxime	Cefdinir
	Ceftizoxime	Cefixime
	Ceftriaxone	Ceftibuten
Fourth	Ceftazidime	Cefpodoxime
	Cefaperazone	
	Cefepime, Cefpirome	

- Chemically they are composed of dihydrothiazine ring and beta-lactam ring.
- They are derived from cephalosporin-C and have a wider spectrum of activity than penicillins

Mechanism of action

- Like penicillin they (Cephalosporins) also act by inhibiting the bacterial cell wall peptidoglycan synthesis. However they bind to different protein than those to which bind penicillin, i.e. instead of **PnBP** they have **CBP**.
- They resist attack by beta-lactamases. They are inactivated by cephalosporinase enzyme.

Classification

The antibacterial activity of different cephalosporins is widely variable. Depending on this they are classified as under:

First Generation Cephalosporins

- First generation cephalosporins are very effective against gram-positive organisms.
- Cephalothin* is resistant to penicillinase, hence can be used in staphylococcal infections.
- Cephadrine* is used for the treatment of infectious diarrhea
- Cefazolin's* has good tissue penetrability: therefore used for **surgical prophylaxis**.

- Cephalexin* is used orally for minor infections like abscesses or cellulitis. It is one of the most commonly used cephalosporins.

Second Generation Cephalosporins

- Second generation cephalosporins are more active against some gram-negative organisms compared to first generation cephalosporins.
- H. influenzae*, *E. coli*, *Proteus* and *Klebsiella* are inhibited.
- Cefuroxime** is resistant to β -lactamases; attains good CSF concentration and is useful in **meningitis**.

Third Generation Cephalosporins

- Third generation cephalosporins are highly resistant to β -lactamases.
- They have good activity against gram-negative organisms. But they are not so active against anaerobes.
- Many of them cross BBB and are useful in **meningitis**.
- Ceftriaxone* has a long $t_{1/2}$ and can be given once daily. It is excreted mainly through biliary tract and no dosage adjustment is needed in renal insufficiency. It can be used in the treatment of **Gonorrhea** (250 mg).
- Ceftazidime* and *cefoperazone*: Effective against *Pseudomonas*

Fourth Generation Cephalosporins

- Cefepime and Cefpirome are the fourth generation agents having activity similar to 3rd generation ones except that they are more resistant to β -lactamases and are effective against organisms resistant to other cephalosporins.
- They attain very good CSF levels and are used in serious gram-negative infections.

Pharmacokinetics

- Some cephalosporins (e.g. cephalexin, cefadroxil, cephadrine, cefaclor, cefuroxime, cefixime) are absorbed orally. Most others have to be given intravenously.
- Intramuscular injections are painful and avoided.
- These drugs are excreted in the urine except cefoperazone and ceftriazone which are excreted through bile.
- Probenecid blocks the renal excretion of cephalosporins.

Resistance

- Resistance is there as in the case of penicillins.
- Resistance is due to
 - Production of specific β -lactamases by bacteria.

Table 12.3.3: Preparation, doses and routes of administration of cephalosporins

Drugs	Doses	Routes
Cefuroxime axetil (CEFTUM)	1-2 gm q 6 h	IV
Cefazolin (ALCIZON)	0.5-1 gm q 6 h	IM/IV
Cephalexin (SPORIDEX)	0.25-1 gm QID	Oral
Cefadroxil (DROXYL)	0.5-1 gm BID	Oral
Cefamandole (KEFADOL)	0.5-2 gm q 4-8 h	IM/IV
Cefuroxime (SUPACEF)	0.75-1.5 gm q 8 h	IM/IV
Cefuroxime axeti (CEFTUM)	0.25-0.5 gm BD	Oral
Cefachlor (KEFLOR)	0.25-0.5 gm q 8 h	Oral
Cefotaxime (OMNATAX)	1-2 gm q 8 h	IM/IV
Ceftriaxone (OFRAMAX)	1-2 gm q 12-24 h	IM/IV
Cefoperazone (CEFOBID)	1-2 gm q 8-12 h	IM/IV
Cefixime (CEFSPAN)	0.2-0.4 gm q 12 h	Oral
Cefpirome (CEFROM)	1-2 gm q 12 h	IV

- Altered target proteins (CBP)
- Development of impermeability to antibiotic determine resistance to cephalosporins.

Therapeutic uses of cephalosporins

1. Alternative to penicillin G
2. **Gram-negative infections:** Urinary, respiratory and soft tissue infections due to gram-negative organisms respond.
3. **Meningitis Due to *H. influenza*:** 3rd generation agents are used.
4. **Surgical prophylaxis:** Cefazolin is used.
5. **Mixed aerobic-anaerobic infections**—common following pelvic surgeries—3rd generation agent in used.
6. **Gonorrhea:** Ceftriaxone (single dose 250 mg) is the drug of choice.
7. **Typhoid:** As alternative to ciprofloxacin.
8. **Nosocomial infections:** Can be treated with 3rd generation cephalosporins.

Adverse reactions

Cephalosporins are generally well-tolerated.

1. **Pain** at the injection site may occur.
2. **Diarrhea** can result from some of the cephalosporins.
3. **Hypersensitivity** reactions like skin rashes, fever, serum sickness and rarely anaphylaxis are seen. 20% of patients allergic to penicillin show cross-reactivity to cephalosporins. There are no reliable skin tests for testing allergy.

4. **Nephrotoxicity** is noted with some cephalosporins. Combination with other nephrotoxic drugs should be avoided.

5. **Bleeding** is due to hypoprothrombinemia which is more common in malnourished patients.

6. **Low WBC count** may be seen though rarely.

7. **Disulfiram like reaction** with alcohol is reported with some cephalosporins.

Preparation, doses and routes of administration of some of the common cephalosporins are given in Table 12.3.3.

OTHER BETA-LACTAM ANTIBIOTICS

CARBAPENEMS

Imipenem: It is beta-lactam antibiotic. It is not inactivated by beta-lactamase enzyme. It is given intravenously because its oral bioavailability is erratic and poor. It is widely distributed in body tissues and fluids. It is inactivated by dihydropeptidase of renal tubules. So it is given in combination with cilastin, an inhibitor of dihydropeptidase. This combination is used to treat infections caused by gram-positive and gram-negative aerobes and anaerobes. Common adverse reactions are gastrointestinal tract upsets, allergic reactions, confusion and convulsions.

MONOBACTAMS

Aztreonam, carumonam and tigemonam are monobactams. They are resistant to beta-lactamases. Out of these, aztreonam is used clinically intravenously. It is active against gram-negative rods including *Hemophilus*,

Neisseria, and *Pseudomonas*. It is not effective against gram-positive bacteria and anaerobes. Adverse drug reactions are allergy, gastrointestinal upsets, hepatitis, and blood dyscrasias.

BETA-LACTAMASE INHIBITORS

Clavulanic acid, Sulbactam and Tazobactam are beta-lactamase inhibitors. They do not have any antimicrobial activity. They protect penicillins from degradation by binding covalently to beta-lactamase. So they are employed in combination with penicillins (ampicillin, amoxicillin, or

ticarcillin) for treating beta-lactamase producing organisms, such as *H. Influenzae*. The combination in use are:

- Amoxicillin + clavulanic acid
- Ampicillin + sulbactam
- Ticarcillin + clavulanic acid
- Piperacillin + tazobactam

These drugs do not inhibit beta-lactamase produced by *Pseudomonas aeruginosa* and *Enterobacter* species. Further, methicillin resistant staphylococci are not susceptible to these drugs.

Broad Spectrum Antibiotics

BROAD SPECTRUM ANTIBIOTICS

Tetracyclines

- The tetracycline are broad spectrum antibiotics.
- Tetracyclines are obtained from the soil actinomycetes, first one is chlortetracycline (aureomycin) in 1948, due to its golden color.
- They have different chemical structures and are produced by different species of *Streptomyces*.
- They are effective against gram (+ve) and gram (–ve) bacteria including anaerobes, Spirochaetes. In addition to bacteria, tetracycline also inhibit the growth of other microorganisms like rickettsiae, chlamydiae, mycoplasma and some protozoa. **Therefore, they are called broad spectrum antibiotics.**
- They differ from penicillin and streptomycin in same respect that they are orally active and has broad spectrum activity.
- Two serious limitations of these drugs are:
 1. Bacteriostatic activity and
 2. Significant adverse drug reactions

Chemistry

Tetracycline is the antibiotics with four cyclic rings (hence the name) and its congeners are derivatives of the polycyclic naphtha-acene-carboxamide.

- All tetracycline are bitter, they are weak water soluble, but their salt with HCl are highly soluble
- The newer members are having higher solubility and potency.

Classification

Tetracyclines (Gp 1)	Semisynthetic tetracyclines (Gp 2)	(Gp 3)
Chlortetracycline	Demeclocycline	Doxycycline
Tetracycline	Methacycline	Minocycline
Oxytetracycline	Lyme cycline	

Spectrum of activity

- It is broad including gram-positive and gram-negative organisms like *Streptococci*, *Staphylococci*, *Gonococci*, *Meningococci*, *H. influenza*, *Brucella*, *V. cholerae*, *Campylobacter*, *Y. pestis* and many anaerobes.
- They inhibit *Rickettsiae*, *Chlamydiae*, *Mycoplasma*, *Actinomyces*, *E. histolytica* and *Plasmodia*.
- They also inhibit spirochets like : *Treponema pallidum* and *T. borrelia*
- Many organisms have now become resistant.

Pharmacokinetics

- Tetracyclines are adequately but absorbed from the gastrointestinal tract, particularly from the stomach and upper small intestine. Older agents absorbed 100% in empty stomach. Newer compound totally absorbed.
 1. Absorption is impaired by food, especially milk and milk products, by aluminum hydroxide gels, by calcium and magnesium salts, antacids and iron. **The cations in these substances chelate with tetracycline, preventing gastrointestinal absorption.**
 2. Minocycline and doxycycline are exceptions in that they chelate poorly with calcium, and food does not interfere with their absorption. However, like other tetracyclines, they do chelate with iron to form insoluble complexes.
- The tetracyclines diffuse readily into body fluids and bind to plasma proteins to varying degrees, depending on the particular preparation. Concentrations in the

- cerebrospinal fluid are about 25%, one fourth of the serum levels unless the meninges are inflamed.
- They have wide distribution ($V_d = >1$ Lit/kg) and the drug is concentrated in liver, spleen, connective tissue of bone-teeth specially bind with mitochondrial protein.
 - Excretion occurs primarily via the kidney, although there is some fecal excretion. Renal clearance of these drugs is by glomerular filtration.
 - The doxycycline is partly metabolized and is removed from the blood by the liver and are excreted into the intestine through the bile. It undergo enterohepatic circulation.

Mechanism of action (Fig. 12.4.1)

- Tetracyclines are primarily bacteriostatic, inhibiting protein synthesis by binding to 30 S ribosome.
- Tetracycline enters the microorganisms partly by passive diffusion through the hydrophilic channels and partly by energy dependent active transport. They bind reversibly

to 30-S subunit of the bacterial ribosome. Due to this, all tetracycline act by ***inhibiting bacterial protein synthesis by blocking the attachment of aminoacyl tRNA to the receptor site on mRNA-ribosome complex.*** (Fig. 12.4.1)

- Since the binding to ribosome is reversible, they are bacteriostatic.

Bacterial resistance

- Bacterial resistance:** may develop which is primarily plasmid-mediated and is an inducible trait.
- Gram-positive bacteria often become resistant to the tetracyclines, limiting the usefulness of these drugs.
- Complete cross-resistance among the tetracycline group of drugs is present.
- Resistance may be due to:
 - Decreased accumulation of tetracycline because the permeability barrier of the cell envelope not allowing tetracycline to concentrate intracellularly.

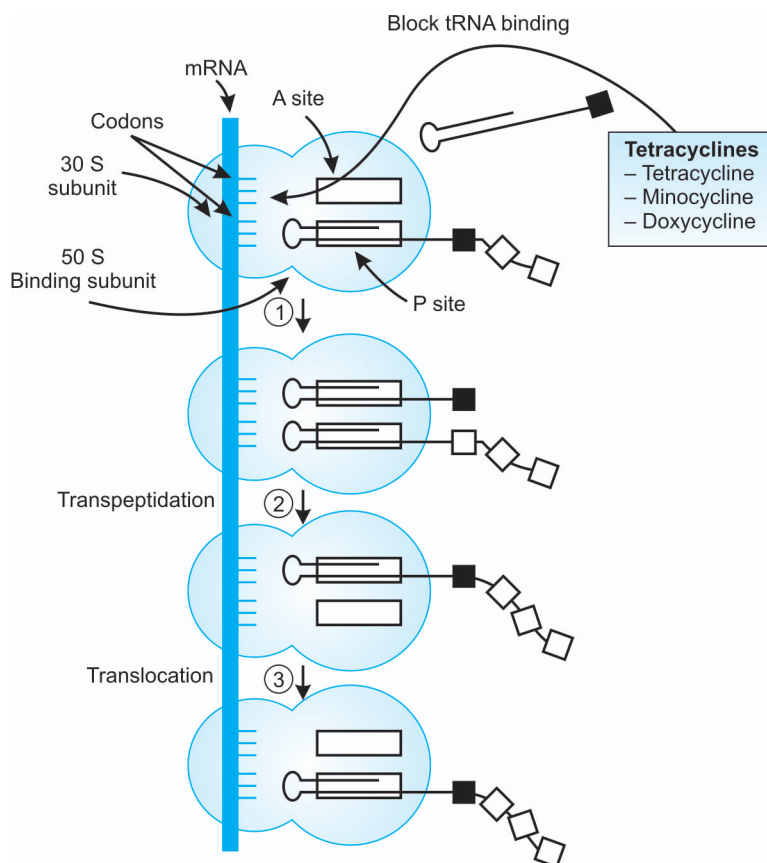


Fig. 12.4.1: Mechanism of action of tetracycline

2. Presence of ribosome protection proteins which decrease access of tetracycline to the ribosome.
3. Inactivation of tetracycline by enzyme.

Therapeutic indications

A. Tetracyclines are the drugs of choice in

1. **Rickettsial infections:** All rickettsial infections respond to tetracyclines.
2. **Chlamydial infections:**
 - lymphogranuloma venereum: given for 2 weeks
 - trachoma—both topical and oral
 - inclusion conjunctivitis.
3. **Atypical Pneumonia:** Due to *Mycoplasma pneumoniae*.
Tetracyclines reduce the duration of illness and are to adjuvant value.
4. **Brucellosis:** Doxycycline 200 mg + Rifampicin 600 mg daily for 6 weeks is the treatment of choice.
5. **Plague:** Tetracyclines may be combined with an aminoglycoside.
6. **Leptospirosis:** Doxycycline 100 mg OD for seven day is the drug of choice for prophylaxis

B. Tetracyclines are useful in other infections like

1. **Traveller's diarrhea:** Doxycycline reduces the incidence of traveller's diarrhea.
2. **Sexually transmitted diseases (STD):** Like syphilis, gonorrhea and chancroid also respond to tetracycline: but are not preferred.
3. **Acne:** The infectious bacteria in the sebaceous follicles metabolize lipids into irritating free fatty acids which trigger the development of acne. Tetracyclines inhibit these bacteria. Low doses are given for a long time (250 mg BD for 4 weeks).

4. Protozoal infections:

5. **Amebiasis:** Tetracyclines are useful in chronic intestinal amoebiasis
6. **Malaria:** Doxycycline is given with quinine in multi-drug resistant malaria.

Adverse effects

1. **Effect on teeth and bones:** Tetracycline chelates calcium. The calcium—tetracycline orthophosphate complexes get deposited in the developing teeth and bones. The deformities depend on the time of tetracycline administration.
2. **Hepatotoxicity** may result in jaundice. Acute hepatic necrosis may occur in pregnant women but is rare.
3. **GIT:** Gastrointestinal irritation, nausea, vomiting and diarrhea—tetracyclines are to be given with food to minimize these effects.
4. **Renal toxicity:** Renal failure may be aggravated. Outdated tetracycline cause a syndrome like Fanconi's syndrome with vomiting, polyuria, proteinuria, glycosuria and acidosis due to metabolites of the outdated tetracyclines.
5. **Phototoxicity:** Skin reactions and dermatitis on exposure to sun are more likely with doxycycline and demeclocycline.

Tetracyclines are thus teratogenic

- **Superinfections:** Since the intestinal flora are extensively suppressed by tetracyclines, these are the most common antibiotics to cause *superinfections*.
- Hypersensitivity reactions are not very common.

Contraindications

Tetracyclines are contraindicated in pregnancy, lactation and in children up to 8 years of age.

Period	Structure affected	Deformity
• Mid pregnancy to 5 months are more susceptible to caries	Deciduous teeth	Brownish discoloration, ill formed and of postnatal life
• 2 month to 5 years of age	Permanent teeth	Pigmentation, discoloration
• Pregnancy and childhood up to 8 years of age	Skeleton	Depressed bone growth

Dosage of some tetracyclines

Tetracyclines	Doses
Chlortetracycline (AUREOMYCIN)	250-500 mg QID
Tetracycline (HOSTACYCLING)	250-500 mg QID
Doxycycline (DOXYCAPS)	200 mg initially then 100 mg OD
Minocycline (CYANOMYCIN)	200 mg initially then 100 mg OD

Doxycycline and Minocycline

They are semisynthetic tetracyclines.

- Given orally they are 95% and 100% absorbed respectively
- Food does not interfere with their absorption
- Have long $t_{1/2}$: It can be given once daily
- Excreted through gut hence can be given in renal impairment
- Minocycline causes vestibular toxicity.
- Minocycline absorption is not impaired by food or calcium ion.
- Demeclocycline has a greater acid and alkaline stability and slower rate of excretion than most tetracyclines; therefore, it produces higher and more prolonged blood levels.
- Methacycline is absorbed rapidly.

CHLORAMPHENICOL

- Chloramphenicol is a broad spectrum antibiotic originally obtained from *streptomyces venezuelae* in 1947. Now it is manufactured entirely by synthetic process.

- It is Yellow/white solid crystals
- Bitter and need protection from light.

Chemistry

It is a nitrobenzene derivative.

Pharmacokinetics

1. Chloramphenicol is absorbed rapidly from the gastrointestinal tract.
2. Plasma protein binding is 50 to 60%, and widely distributed in the body.
3. It is widely distributed in body fluids and reaches therapeutic levels in cerebrospinal fluid. It is also present in bile, milk, and aqueous humor.
4. Chloramphenicol is metabolized in the liver by glucuronyl transferase.
5. Its metabolites are excreted in the urine.

Mechanism of action (Fig. 12.4.2)

- Chloramphenicol is bacteriostatic but to some organisms it is bactericidal.
- It acts by inhibiting bacterial protein synthesis by binding at 50S ribosomal level.

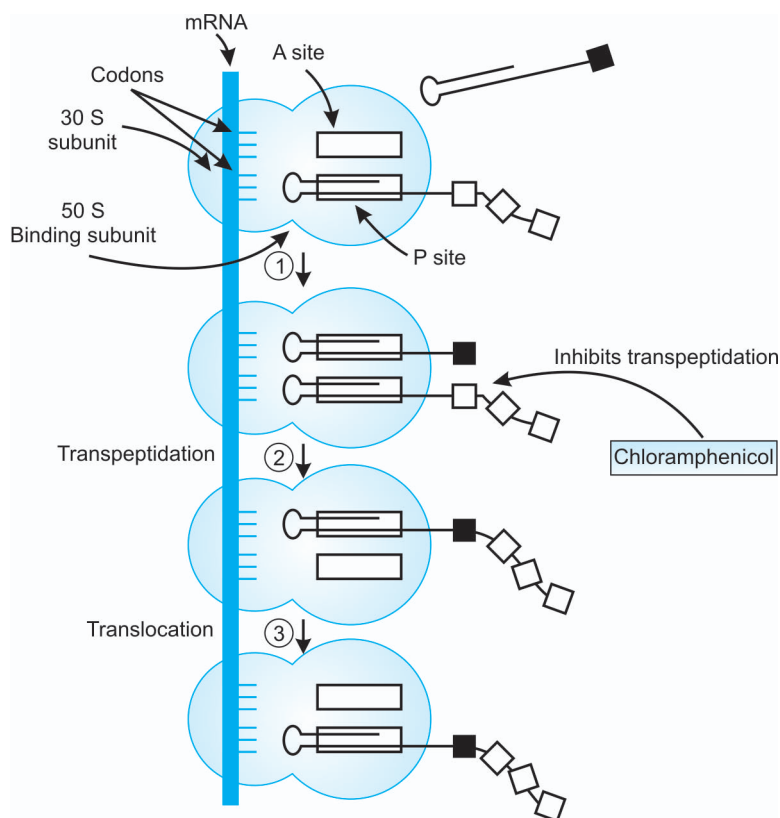


Fig. 12.4.2: Mechanism of action of chloramphenicol

Antibacterial spectrum

- It is broad spectrum and includes gram-negative organisms, some gram-positive organisms, anaerobic bacteria, *rickettsiae*, *chlamydiae* and *mycoplasma*.
- Highly active against *salmonella* and *S. typhi*.
- Highly active against *H. Influenza*, *B. Pertusis*, *Klebsiella* and anaerobes: *bact. Fragilis*.
- Less active against gram positive cocci, *spirochetes*, *enterobacter*, *antamoeba* and *plasmodium sp.*
- Inactive against *pseudomonas*, *mycobacteria*, *proteus*, *virus* and *fungi*.

Resistance

Bacterial resistance to chloramphenicol develops slowly. It is plasmid mediated (due to transfer of R factor by conjugation) and may be due to:

1. Reduced permeability of the microorganisms
2. Production of an enzyme (acetyl transferase) by R plasmid of gm (–ve) bacteria
3. Ribosomal insensitivity.

Therapeutic indications

Because of the risk of bone marrow toxicity and availability of safer drugs, chloramphenicol is not generally preferred. The indications are:

1. **Typhoid fever:** Very effective in typhoid; given for 14 days (500 mg QID till fever subsides then 250 mg QID up to 14th day).
2. **Bacterial meningitis:** In *H. influenzae* and meningococcal meningitis: chloramphenicol is an alternative to penicillin.
3. **Anaerobic infections:** Chloramphenicol + penicillin + an aminoglycoside can be used in severe anaerobic infections as an alternative to metronidazole and clindamycin.
4. **Eye infections:** Chloramphenicol is used topically because of the good penetration into aqueous humor.
5. **Rickettsial infections:** As an alternative when tetracyclines are contraindicated.

Adverse reactions

- Gastrointestinal disturbances: Nausea, vomiting, diarrhea.
- Hypersensitivity reactions can occur.
- The most important effect, which may be related to hypersensitivity, is bone marrow depression, resulting in pancytopenia.
 - a. The Bone marrow depression is of two types:
 - *Dose-dependant:* anemia, leukopenia and thrombocytopenia.
 - *Idiosyncratic response*—resulting in aplastic anemia which may be fatal. It may be due to a toxic metabolite.
 - b. It is usually associated with prolonged therapy and more than one episode of treatment with chloramphenicol.
 - c. It occurs in 1 in 40,000 patients given chloramphenicol and often is fatal.
- Reversible blood dyscrasia may also occur which is dose dependent
- **Superinfections** can occur, including oropharyngeal candidiasis and acute staphylococcal enterocolitis.
- **Gray-body syndrome** is seen in neonates, especially premature infants (baby), who have been given relatively large doses of chloramphenicol. (> 100 mg/kg)
 1. Cyanosis, relatively irregularities, vasomotor collapse, abdominal distention, loose green stools, and an ashen-gray color characterize this often fatal syndrome.
 2. The condition develops because of the immature hepatic conjugating mechanism and the inadequate mechanism for renal excretion in neonates.

Drug interactions

- Chloramphenicol inhibits hepatic microsomal enzymes and thereby prolongs the half-life of drugs metabolized by this system.
- This may result in enhanced toxicity of some drugs like phenytoin, tolbutamide and dicumarol.

Aminoglycosides

- Aminoglycoside antibiotics contain amino-sugars in glycosidic linkage. Drugs included in this group are:

<i>Streptomycin</i>	<i>Paramomycin</i>
<i>Kanamycin</i>	<i>Gentamicin</i>
<i>Tobramycin</i>	<i>Amikacin</i>
<i>Neomycin</i>	<i>Netilmicin</i>
<i>Spectinomycin</i>	
- They are derived from the soil actinomycetes.
- Except gentamicin, all other antibiotics are derived from the genus *Streptomyces*.
- Gentamicin is produced by the mould *Micromonospora purpurea*.

Antibacterial spectrum

- Aminoglycosides have a narrow spectrum of activity.
- They are effective mainly against aerobic gram-negative bacilli like *E. coli*, *Proteus*, *Brucella*, *Salmonella*, *Shigella* and *Klebsiella*.
- Mycobacterium tuberculosis* infection responds to streptomycin and kanamycin, while amikacin, gentamicin and tobramycin are active against *Streptococcus fecalis* and *Pseudomonas aeruginosa* also.

General features about aminoglycosides

- All these drugs share many chemical, antimicrobial, pharmacological and toxic characteristics.

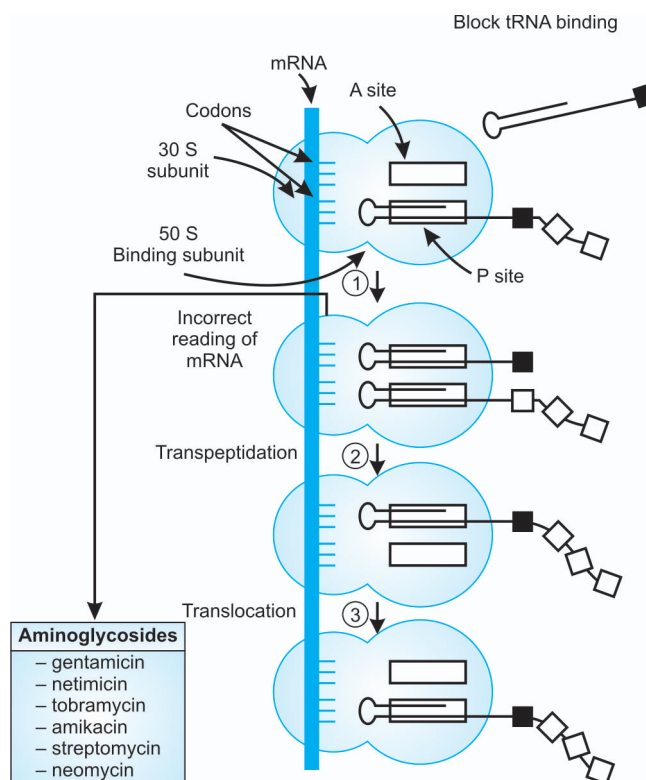


Fig. 12.5.1: Mechanism of action of aminoglycosides

- Absorption of aminoglycosides from gastrointestinal tract is poor. However, they are rapidly absorbed from intramuscular and subcutaneous sites of injection.
- They reach to all body fluids but do not cross the blood-brain barrier. So they do not reach the CSF or eye.
- They produce variable degree of ototoxicity and nephrotoxicity as adverse effects.
- Neomycin is not used systematically. It is applied topically.
- Aminoglycosides are not metabolized. They are excreted unchanged by the kidneys.

Mechanism of action (Fig. 12.5.1)

- They are all bactericidal.
- Aminoglycoside antibiotics act directly on the bacterial ribosomes (30S) where, they inhibit bacterial protein synthesis and decrease translation of genetic code.
- They are bactericidal. Higher the concentration, greater is the bactericidal effect.
- A residual bactericidal effect: postantibiotic effect: remains even after the plasma levels of aminoglycosides fall. Hence, even though they have a short $t_{1/2}$, they can be given once a day.
- Aminoglycosides are water soluble and more active at alkaline pH probably due to improved transport of the antimicrobial agents inside the bacterial cell.
- Human ribosomes are unaffected.

Resistance to aminoglycosides is acquired by

1. Development of resistance against aminoglycosides is very common in gram-negative bacteria and mycobacteria
2. Low affinity of ribosome's acquired by mutation.
3. Decrease in permeability to the antibiotic.

There is partial cross-resistance among various aminoglycosides.

Doses and routes of administration

Doses and routes of administration of important aminoglycosides are given in Table 12.5.1.

Adverse effects

1. Ototoxicity

- It is the most important toxicity. Both vestibular and auditory dysfunction can occur depending on the dose and duration.
- *Ototoxicity includes:* (cochlear damage - tinnitus, hearing disturbances, complete deafness; vestibular

Table 12.5.1: Doses and routes of administration of aminoglycosides

Aminoglycosides	Doses	Routes
Streptomycin (STREPTONEX)	1-2 g/day	IM
Gentamicin (GARAMYLCIN)	3-5 mg/kg/day in 3 divided doses	IM/IV
Tobramycin (TOBRANEG)	3-5 mg/kg/day in 3 divided doses	IM/IV
Amikacin (AMICIN)	15 mg/kg/day in 2-3 divided doses	IM/IV
Netimicin (NETROMYCIN)	4-6 mg/kg/day in 2-3 divided doses	IM/IV

damage- vertigo, nystagmus, balancing problem and ataxia).

- The aminoglycosides get concentrated in the labyrinthine fluid of the inner ear and damage both cochlear hair cells and vestibular sensory cells.
 - As the cochlear cells cannot regenerate, there is progressive, permanent deafness. Tinnitus appears first, followed by deafness; elderly people are more susceptible.
 - Stopping the drug can prevent further damage. Vestibular dysfunction is manifested by headache, nausea, vomiting, dizziness, vertigo, nystagmus and ataxia. Recovery is slow over 1-2 years.
 - Streptomycin, gentamicin, and tobramycin mainly affect vestibular function whereas cochlear function is mainly affected by kanamycin, amikacin and neomycin.
 - They should be given carefully to pregnant mothers because they cross the placenta and can cause fetal eighth nerve damage.

2. Nephrotoxicity

- Aminoglycosides attain high concentration in the renal cortex and cause damage to the renal tubules. These drugs may lead to tubular necrosis.
- Nephrotoxicity is enhanced by simultaneously use of loop diuretics or cephalosporins with aminoglycosides results in loss of urine concentrating capacity, low GFR and albuminuria. These effects are reversible.

3. Neuromuscular blockade

- Aminoglycoside antibiotics possess *neuromuscular blocking property* (curare-like effects). So rarely they may lead to skeletal muscular weakness and respiratory weakness. These drugs, therefore, should not be used in patient with myasthenia gravis or along with neuromuscular blocking agents.

Precautions in using aminoglycosides

- Contraindicated in pregnancy.
- To be used cautiously in elderly, in renal damage and in combination with skeletal muscle relaxants.
- Avoid concurrent use of other ototoxic drugs like loop diuretics.
- Avoid concurrent use of other nephrotoxic drugs like amphotericin B, cephalothin and cisplatin.
- Do not mix aminoglycosides with any other drug in the same syringe.
- Determination of plasma levels of aminoglycosides may be needed in severe infections and in patients with renal dysfunction.

Streptomycin

- It is obtained from *Streptomyces Griseus* is mainly effective against aerobic gram-negative bacilli.
- When used alone, bacteria, especially the tubercle bacillus rapidly develops resistance to it. Streptomycin is the least nephrotoxic among aminoglycosides.

Therapeutic indications

1. **Plague, tularaemia and brucellosis** — streptomycin is given with a tetracycline
2. **Tuberculosis**
3. **Subacute bacterial endocarditis (SBE)** — Combination of streptomycin and penicillin is synergistic in this condition.

Gentamicin

- It is obtained from *micromonospora purpurea* is more potent and has a broader spectrum of action compared to streptomycin.
- Development of resistance has limited its use.

Therapeutic indications

1. Gentamicin may be used in place of streptomycin.
2. **UTI:** Gentamicin is effective in uncomplicated UTI as it is released for a long time from the renal cortex.
3. **Pneumonia:** Due to gram-negative organisms may be treated with gentamicin + penicillin.
4. **Meningitis:** Due to gram-negative bacilli, gentamicin is used with a 3rd generation cephalosporin.
5. **Osteomyelitis, peritonitis, septicemia:** caused by gram-negative organisms can be treated with gentamicin.

Gentamicin cream is used topically in burns and other infected wounds. Gentamicin eye drop is used in bacterial conjunctivitis.

Kanamycin

Now days due to its toxicity, its use is limited to multi-drug resistant tuberculosis. It can also be used for local application.

Tobramycin

In most of the features, tobramycin resembles gentamicin, therefore clinically it is interchangeable with gentamicin. It is found to be very active against *Pseudomonas* and is therefore used with an antipseudomonal penicillin in such infections.

Amikacin

It is a derivative of kanamycin. Among all the aminoglycosides, it has the widest antibacterial spectrum. It is resistant to aminoglycoside inactivating enzymes.

Therapeutic indication

1. Amikacin is useful in multidrug resistant tuberculosis in combination with other drugs. It is also used in infections due to atypical mycobacteria in patients with AIDS.
2. Nosocomial infections due to gram-negative organisms

Netimicin

Netimicin is used in serious infections due to gram-negative bacilli. Like amikacin, netimicin is also resistant to aminoglycoside inactivating enzymes.

Sisomicin

In terms of actions, toxicity and uses it is more or less similar to gentamicin.

Neomycin

- Its antibacterial spectrum is wide. As it is highly ototoxic, it is not given systemically.
- It is used topically as ointments, creams and powder.

Adverse effects

- Neomycin can cause skin rashes on topical use.
- Oral use can cause diarrhea, steatorrhea and malabsorption.
- Superinfection with *Candida* can also occur.

Therapeutic indications

1. **Orally**—neomycin is not absorbed when given orally. It is used to prepare the bowel for surgery, i.e. for preoperative gut sterilization.

2. **Hepatic coma**—colonic bacteria produces ammonia which is absorbed and converted to urea by the liver. In severe hepatic failure, as liver is unable to handle this NH_3 , blood NH_3 levels rise resulting in encephalopathy. As neomycin inhibits intestinal flora, NH_3 production falls.
3. Neomycin is used topically in skin infections, burns, ulcers and wounds; eye and ear infections.

Spectinomycin

- It is rather an aminocyclitol
- Spectinomycin is related to aminoglycosides and is effective against gram-negative bacteria.
- It is used only in gonorrhea (2gm IM) in patients allergic to penicillin and quinolones.

Macrolides and Other Antibiotics

MACROLIDES

- These are the antibiotics with a macrocyclic lactone ring to which sugars are attached.
- Macrolides includes: Erythromycin and its semisynthetic derivatives roxithromycin, clarithromycin, azithromycin and recently introduced dirithromycin, etc.

ERYTHROMYCIN

- In 1952, Erythromycin was first discovered. It was obtained from *Streptomyces erythreus*.

Antibacterial spectrum

- The antibacterial spectrum is similar to that of penicillin.

- They are effective against gram (+ve) organisms (*Streptococci*, *Pneumococci*, *Staphylococci*, *Corynebacteria*, *Gonococci* and *Anthrax*) and gram (–ve) organisms (*Neisseria*, *Helicobacter*, *Legionella*, *Mycoplasma*, *Chlamydia*, *Spirochaetes*).
- *C. diphtheriae*, *C. jejuni*, and some atypical *Mycobacteria* are sensitive.

Mechanism of action (Fig. 12.6.1)

- Erythromycin is bacteriostatic at low and cidal at high concentrations.
- They act by inhibiting bacterial protein synthesis at 50S ribosome subunits and interferes with 'translocation'.

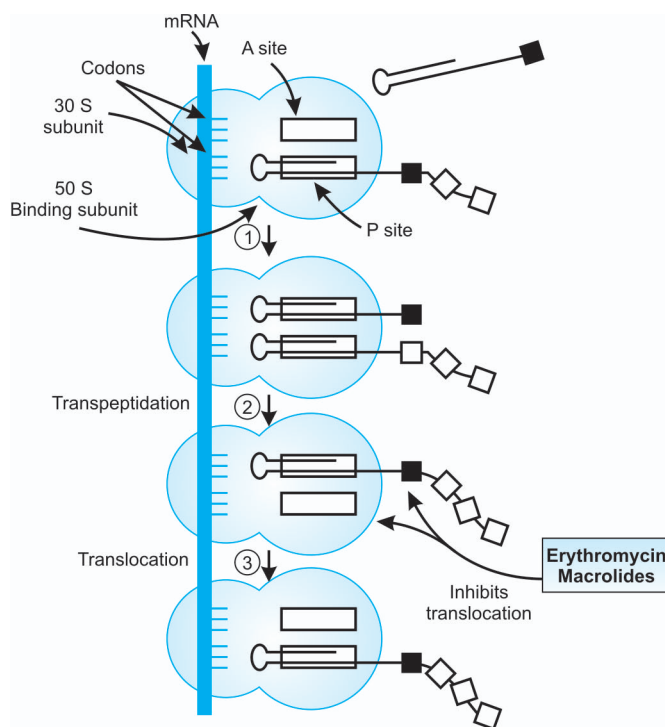


Fig. 12.6.1: Mechanism of action of Macrolides

Resistance

Bacterial resistance to erythromycin is common especially amongst staphylococci. Resistance to macrolides is acquired through plasmids (extrachromosomal genetic material). The mechanism involved may be:

- Low permeability of the bacteria to the antibiotic
- Low affinity of ribosomes to macrolides.
- Production of inactivating enzymes

Pharmacokinetics

- They are readily absorbed on oral administration.
- Erythromycin is acid labile, i.e. destroyed by gastric acid and is therefore given as enteric coated tablets.
- So acid stable preparations such as stearate, succinate, estolate esters of erythromycin or enteric coated tablets are used.
- Good concentration is attained in most fluids except brain and CSF.
- Erythromycin is primarily excreted in the bile and thus appear in the feces; adjustment is not needed in renal failure.

Therapeutic indications

Erythromycin can be used as an alternative to penicillin in patients allergic to penicillin.

- 1. Whooping cough:** Erythromycin is the drug of choice for both prophylaxis and treatment.
- 2. Streptococcal infections:** Tonsillitis pharyngitis, and scarlet fever can be treated with erythromycin.
- 3. Atypical pneumonia:** Due to *Mycoplasma pneumoniae*: erythromycin is the Drug of Choice (DOC).
- 4. Legionnaire's pneumonia:** Erythromycin should be given for 10-14 days as a treatment.
- 5. Staphylococcal infections:** Various minor infections can be treated.
- 6. Diphtheria:** Antitoxin is life saving, yet erythromycin is very effective in acute stage. Erythromycin also eradicates carrier state.
- 7. Anthrax:** Erythromycin is an alternative to penicillin.
- 8. Campylobacter gastroenteritis:** As an alternative to fluoroquinolones.
- 9. Syphilis and gonorrhea:** Erythromycin is used as an alternative.
- 10. Tetanus:** Erythromycin eradicates carrier state.
- 11. Topical:** Erythromycin ointment is used for skin infections and boils.

Limitations of Erythromycin

- Narrow spectrum
- Gastric intolerance
- Acid labile
- Low oral bioavailability
- Poor tissue penetration
- Shorter half-life

Adverse effects

- Nausea, vomiting and abdominal cramps mimic acute cholecystitis, are the minor adverse effects.
- **Hepatitis with cholestatic jaundice:** Starts after 2-3 weeks of treatment and is more common with the estolate salt. The condition is reversible, i.e. the patient recovers on stopping the drug.

Drug Interaction

- Erythromycin inhibits the hepatic metabolism of carbamazepine, terfenadine, theophylline, valproate, digoxin and warfarin thereby raises the plasma levels and resulting in toxicity due to these drugs.

Newer macrolide derivatives have been synthesized. They have better pharmacokinetics and lower incidence of adverse drug reactions. However, antibacterial spectrum is same.

Roxithromycin

- It is longer-acting, acid stable, more potent, better absorbed and has better tissue penetrability compared to erythromycin.
- It does not inhibit the metabolism of other drugs; hence drug interactions are avoided. It should be taken 30 minutes before food.
- It can be used as an alternative to erythromycin but is more expensive.

Clarithromycin

- Compared to erythromycin, clarithromycin is longer-acting, acid stable, better absorbed and better tolerated;
- It is more effective against a typical mycobacteria, *H. pylori* and some protozoa.

Therapeutic indications

- As a component of triple drug regimen to eradicate *H. pylori* infection
- As first line drug in the combination regimen for *Mycobact. avium* complex (MAC) infection in AIDS patients

- As second line drug for other atypical mycobacterial diseases as well as leprosy.

Though clarithromycin is effective in other indications of erythromycin, its higher cost makes it less preferable.

Azithromycin

- It is an azalide, is a derivative of erythromycin with activity similar to clarithromycin.
- It is acid stable, rapidly absorbed, has better tissue penetrability, and is longer-acting and better tolerated than erythromycin.

Uses

- Like erythromycin it can be used in respiratory, genital and skin infections and in pneumonia.
- It is used in the prophylaxis and treatment of atypical mycobacterial infections in AIDS patients.

Adverse effect and drug interactions

- Erythromycin may cause allergic reactions (fever, eosinophilia, skin eruptions), epigastric distress (large doses); obstructive type of jaundice may be produced by erythromycin estolate.

- These drugs increase half-life of warfarin, theophylline, digoxin, carbamazepine and cyclosporine by inhibiting cytochrome P-450.

Doses and duration of treatment of some common macrolide antibiotics are given in Table 12.6.1.

Table 12.6.1: Macrolide antibiotics: Dose and duration of treatment

Drug	Dose (oral) and duration
Erythromycin stearate (ERYTHROCIN)	250-500 mg QID 7-14 days
Erythromycin estolate (ALTHROCIN)	250-500 mg QID 7-14 days
Roxithromycin (ROXID)	150 mg BD (to be taken 30 minutes before food)
Clarithromycin (CLARIBID)	250-500 mg BD 7-14 days
Azithromycin (AZITHRAL)	1st day 500 mg OD 250 mg OD for next 3-4 days

Quinolones and Fluoroquinolones

QUINOLONES AND FLUOROQUINOLONES

- The quinolones are a group of synthetic antimicrobial agents.
- Nalidixic acid is a quinolone derivative and is the older agent in the group.
- The other members of the group are oxolinic acid and cinoxacin.
- Since systemic antibacterial levels of 4-quinolone derivatives are not achieved, they are only useful as urinary antiseptic.

Pharmacokinetics

- On oral administration, all the quinolones are well absorbed.
- They also cross the placental barrier.
- 80% of 4-quinolones are metabolized in liver and 20% are excreted in urine in free form.
- It is excreted too rapidly to have systemic effects but attains high concentration in the urine.

NALIDIXIC ACID

- Nalidixic acid was introduced in 1960s.
- It is bactericidal against various gram negative organisms like *Shigella*, *E.coli*, *Klebsiella* and *Proteus*.

Therapeutic indications

- Its use is limited to urinary tract infections and GIT infections due to its lower potency, lower concentration in blood and tissue and higher incidences of bacterial resistance.
- Nalidixic acid is used in uncomplicated UTI and diarrhea due to *Shigella*, *E.coli*, and *Proteus*.

Adverse effects

- CNS effects like headache, myalgia, drowsiness and allergic reactions, hemolytic anemia may occur.

FLUOROQUINOLONES

- The fluorinated quinolones were discovered in 1980s.
- They are characterized with higher potency, wider spectrum of activity, fewer side effects, less chance of resistance and better tissue penetration compared to quinolones.
- The fluoroquinolones include; *Norfloxacin*, *ciprofloxacin*, *pefloxacin*, *ofloxacin*, *lomefloxacin* and *sparfloxacin*. Many more are being added.

Classification

First generation	Second generation
Ciprofloxacin	Lomefloxacin
Norfloxacin	Sparfloxacin
Ofloxacin	Levofloxacin
Pefloxacin	Gatifloxacin
Moxifloxacin	
	Newer: • Acrosoxacin • Cinoxacin

Antibacterial spectrum

- Gram-negative organisms like, *Salmonella*, *Shigella*, *E.coli*, *Enterobacteria*; gram-positive organisms like *staphylococci*; *chlamydiae*, *Mycoplasma*, *Mycobacterium* and anaerobic organisms are susceptible.
- They are not active against *Pseudomonas*.

Pharmacokinetics

- Their absorption is good. They are widely distributed in the body.
- Food and antacids interfere with absorption; they have higher plasma protein binding capability.
- They are partly metabolized in the liver and, are excreted by kidneys.
- Fluoroquinolones attain higher concentration (20–50 times) in urine than plasma therefore DOC (kills pathogen) in UTI.

Mechanism of action

- Fluoroquinolones are bactericidal. They inhibit the bacterial enzyme **DNA Gyrase** which is required for DNA replication and transcription.
- **DNA Gyrase: (A and B):** A is responsible for nicking of DNA, while B is responsible for negative coiling of nicked coil (de-winding).
- DNA Gyrase are of two type **Topoisomerase IV** (bacterial), and **Topoisomerase II** (mammalian).
- Fluoroquinolones have selective action only on Topoisomerase IV, while they have very low affinity for Topoisomerase II that's why they have less toxicity in human beings.

Resistance

- Resistance is comparatively not very common due to the unique mechanism of action of the drug.
- Resistance is due to mutations in the target enzyme or a change in the permeability of the organism.
- Several strains of *E. coli*, *Staphylococci*, *Pseudomonas* and *Serratia* have now developed resistance.

Adverse effects

- Fluoroquinolones are well-tolerated. Adverse effects are infrequent.
- Nausea, vomiting, abdominal discomfort, diarrhea and rashes may be seen.
- Tendinitis with associated risk of tendon rupture has been reported.
- Fluoroquinolones damage the growing cartilage resulting in arthropathy and are therefore contraindicated up to 18 years of age.

- They may produce certain CNS side effects like: Seizures in children, drowsiness, vertigo and visual defect.

Fluoroquinolones are contraindicated in:

1. Children, during pregnancy and lactating mothers, because these drugs may cause arthropathy in infants and children.
2. Patients of epilepsy and cerebral arteriosclerosis, because they may precipitate convulsions. Doses of these drugs should be reduced in presence of renal dysfunction.

Therapeutic indications*a. They are drugs of choice for:*

- **Pseudomonas infections (urinary tract infections and others)**
- **Multi-antibiotic resistant infections**
- **Salmonella infections (enteric fever including carrier state)**
- **Dysentery due to shigella infection**
- **N-Gonorrhea (a single dose is sufficient)**
- **Septicemia (severe infection)**

b. They are alternative drugs for:

- **Infections of bones, joints, and respiratory tract**
- **UTI due to coliform organisms**
- **Pneumonia due to mycoplasma**
- **Falciparum malaria**
- **Plague, cholera, hemophilus infection**
- **Tuberculosis and lepromatous leprosy.**

Special features of fluoroquinolones (Table 12.7.1)

- **Ciprofloxacin:** It is widely used. Dose 250-750 mg/12 hrs orally.

Table 12.7.1: Fluoroquinolones: Dose, route of administration and remark

Drug	Dose and route	Remarks
Ciprofloxacin (CIPLOX)	Oral : 250-750 mg BD IV: 100-200 mg 12 hr	Most widely used fluoroquinolone
Norfloxacin (NORFLOX) infections	Oral: 400 mg BD	Preferred in urinary and genital
Ofloxacin (TARIVID)	Oral : 200-400 mg OD IV: 200-400 mg/ 12-24h	Indicated in urinary and respiratory tract infections and gonorrhea
Pefloxacin (PEFLOX)	Oral: 400 mg BD IV: 400 mg/12h	Penetration into CSF is good
Lomefloxacin (LOMEF)	Oral: 400 mg OD	Has a long $t_{1/2}$
Sparfloxacin (SPARLOX)	Oral: 200-400 mg OD	Enhanced activity against gram +ve organisms and in atypical pneumonia

- **Norfloxacin:** Absorption is partial. Used for urinary tract infection and gonorrhea. Dose 400 mg/12 hrs oral.
- **Pefloxacin:** Its clearance from body is inhibited by cimetidine. Dose 400 mg/12 hrs oral.
- **Ofloxacin:** Its absorption is complete. It does not inhibit hepatic metabolizing enzymes. Dose 200-400 mg/day oral.
- **Acrosoxacin:** It is used in single dose (300 mg) in gonorrhea.
- **Enoxacin:** It is also used in single dose (400 mg) in gonorrhea.
- **Levofloxacin:** It is levo isomer of ofloxacin having improved antibacterial spectrum. It is indicated in community acquired pneumonia and exacerbations of chronic bronchitis. Dose is 500 mg/day oral.
- **Sparfloxacin:** It is difluorinated quinolone which has ciprofloxacin like uses. Dose 200-400 mg orally in one or two divided doses.
- **Lomefloxacin:** It is also difluorinated quinolone which has ciprofloxacin like activity. Dose 400 mg (Single-dose) daily orally.

Chemotherapy of Urinary Tract Infections

CHEMOTHERAPY OF URINARY TRACT INFECTIONS

Treatment of Urinary Tract Infection (UTI)

Urinary tract infections are caused by coliforms (*E.coli*, *Proteus*, *Klebsiella*, *Enterobacter*), *Pseudomonas aeruginosa*, enterococci and *Staph. saprophyticus* commonly.

- Infection of the urinary tract may be acute or chronic.
- UTI can also be classified as Lower UTI: due to gram (+) bacteria and Upper UTIs: usually due to gram (–) bacteria or mixed infection, that's why treatment of Upper UTI is more tricky and difficult.
- They are quite common and sometimes difficult to treat because of rapid emergence of resistant strains and recurrence of UTI in women, enlarged prostate, structural abnormality of urinary tract and due to ineffective treatment.
- A drug will be effective when excreted in urine in active form. Low doses of suitable antimicrobials may be effective in lower urinary tract infection while full dose of a drug is required for upper urinary tract.
- Systemic antimicrobial can be used for upper or lower urinary tract infection while urinary antiseptics are useful for lower urinary tract infection. Following antimicrobials are effective in the treatment of urinary tract infection. They have already been discussed in detail in previous chapters.

Third generation cephalosporins	Carbenicillin
Cotrimoxazole	Gentamycin
Sulphonamides	Nalidixic acid
Ampicillin	Norfloxacin
Trimethoprim	Amoxicillin

Prophylaxis for Urinary Tract Infection

This may be required during:

- Catheterization or instrumentation
- Use of indwelling catheters

- Presence of uncorrectable abnormalities of urinary tract
- Inoperable enlarged prostate
- Urinary stasis due to chronic obstruction

Nitrofurantoin

It is a synthetic nitrofuran derivative

- It is bacteriostatic, but at higher concentrations it may be bactericidal;
- Spectrum: effective against many gram-positive and gram-negative bacteria.
- On oral administration, it is readily absorbed, metabolized and excreted in urine. It is only useful as urinary antiseptic because of its rapid excretion.
- It is used to treat lower urinary tract infection caused by coliforms.
- For acute urinary tract infection, it is given in doses of 100 mg four times a day while
- For chronic urinary tract infection as well as prophylactic agent in recurrent urinary tract infection; it is administered in doses of 100 mg per day. It should be administered with meals.
- **Adverse effect:** It may cause gastric upsets, hemolytic anemia in glucose-6-phosphate dehydrogenase deficiency and rarely neuropathies and allergic reactions. It is contraindicated in renal insufficiency.
- The action of nalidixic acid is antagonized by nitrofurantoin.

Methenamine Mandelate (Mandelamine)

It is a salt of mandelic acid and methenamine. It is employed only as antiseptic for lower urinary tract infection

- It is effective due to formaldehyde released in acidic urine below pH 5.5.
- On oral administration, it is readily absorbed and excreted in the urine.

- For desired effect, urine must be made acidic by giving ascorbic acid (4-12 gm/day).
- Formaldehyde is bactericidal and resistance does not develop to it.
- It is used orally in chronic UTI that is resistant to other drugs.
- It is effective against most of the urinary organisms except proteus because this makes the urine alkaline.
- Sulphonamides should not be given along with it because they form an insoluble compound with formaldehyde. It should not be used in presence of renal and hepatic failure.
- It is kept reserved to treat chronic and recurrent urinary tract infection not responding to other drugs
- Gastritis and cystitis may occur as side effect.

Acidifying agents

- They are required to keep the urine pH acidic while using nitrofurantoin or Methenamine mandelate.

- They also keep down bacteriuria which may be useful in chronic or recurrent urinary tract infection.
- For this purpose, ascorbic acid and ammonium chloride are used.

Urinary analgesic

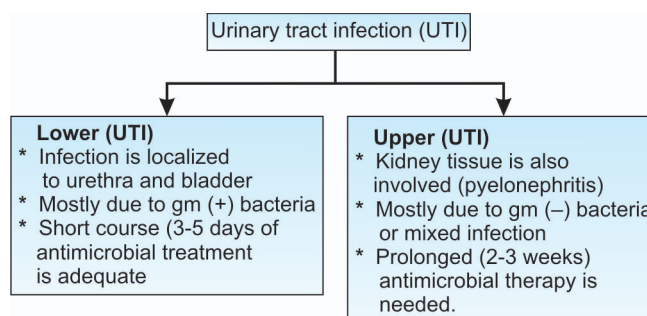
- Phenazopyridine has analgesic action on the urinary tract and relieves burning symptoms of dysuria and urgency.

4-Quinolone

- They are used to treat urinary tract infection caused by *E.coli* and some other coliforms. Nalidixic acid, oxolinic acid and cinoxacin are 4-quinolone which are used to treat lower urinary tract infection as urinary antiseptics.

Prophylaxis for UTI

- Catheterization or instrumentations.
- Urinary stasis due to chronic obstructions.
- Benign prostatic hypertrophy or any abnormalities of urinary tract.



Miscellaneous Antibiotics

MISCELLANEOUS ANTIBIOTICS

Lincomycin and Clindamycin

- Lincomycin is an antibiotic. It is obtained from *streptomyces lincolnensis*. Clindamycin is chlorinated derivative (congener) of lincomycin and is more potent therefore clindamycin is used clinically.
- Clindamycin acts by inhibiting protein synthesis which is due to its attachment with 50 S subunit of bacterial ribosomes
- Clindamycin is readily absorbed from gastrointestinal tract and is widely distributed in the body except CSF. It attains good concentration in the bone and many other tissues.
- It is metabolized in the liver and is excreted in the urine and bile with some enterohepatic circulation. Its metabolites are also active.
- It is effective against gram (+ve) cocci and anaerobes, streptococci, staphylococci, pneumococci, etc.

Therapeutic indications

- Anaerobic infection: It is used in the treatment of severe anaerobic infection caused by bacteroids and other anaerobes. It is combined with an aminoglycoside or cephalosporines to treat mixed infection. Its dose is 150-300 mg /6 hourly daily.
- Clindamycin is also useful in pneumocystis carinii pneumonia and toxoplasmosis in AIDS patients.

Adverse effects

- Common adverse reactions are gastrointestinal upsets, skin rashes and neuromuscular blockade.
- Sometimes, it causes neutropenia and hepatic dysfunction. The most severe reaction is clindamycin associ-

ated pseudomembranous enterocolitis (diarrhea) due to clostridium difficile super infection which is potentially fatal complication. It should be promptly treated with oral vancomycin or metronidazole.

- Intravenous use can cause thrombophlebitis.

Vancomycin

- Vancomycin is glycopeptide and is produced by *Streptococcus orientalis*.
- It is bactericidal and acts by inhibiting cell wall synthesis.
- Vancomycin is not absorbed orally: It is given parentally (IV)
- It is active against gram-positive bacteria particularly staphylococci including those resistant to methicillin.
- It is widely distributed and excreted through urine.

Therapeutic indication

1. *Methicillin resistant staphylococci*: vancomycin is given IV for serious infections like osteomyelitis, endocarditis and soft-tissue abscesses
2. Penicillin resistant pneumococcal infections: vancomycin is prescribed with a cephalosporin.
3. Enterococcal endocarditis: as an alternative to penicillin.
4. Pseudomembranous colitis: oral vancomycin is used.

Adverse effects

- *Common side effect includes*: Skin rashes, pain at the site of injection, thrombophlebitis, ototoxicity and nephrotoxicity.
- Concurrent use of other ototoxic and nephrotoxic drugs should be avoided.
- Dose of vancomycin should be adjusted in renal dysfunction.

Teicoplanin

- It has structural resemblance with vancomycin
- Teicoplanin: It is bactericidal and acts by inhibiting cell wall synthesis.
- It is effective against gram-positive bacteria particularly staphylococci.
- It is given once a day because it has prolonged half-life (50 hours).
- Teicoplanin can be safely given intramuscularly. It is also less toxic.
- Occasionally causes allergic reactions. It is used in osteomyelitis and endocarditis due to methicillin resistant staphylococci and enterococci. TARGOCID 200-400 mg/day.

Bacitracin

- Bacitracin produced by *Bacillus subtilis*.
- It is effective against gram-positive bacteria.
- It is bactericidal and act by inhibiting the cell wall synthesis.
- It is not absorbed orally, it is also too toxic when given systematically and is therefore used only for topical application: skin infections, surgical wounds, ulcers and ocular infections (NEOSPRIN powder is bacitracin + neomycin).

POLYPEPTIDE ANTIBIOTICS**Polymyxin and Colistin**

- Polymyxin obtained from *Bacillus polymyxa*, and colistin from *Bacillus colistinus*.
- They are effective against gram-negative bacteria.
- Polypeptide antibiotics are not absorbed orally; They are also very toxic to be given systemically therefore they are used only topically, but when, applied topically, they may rarely cause skin rashes.

Mechanism of action

- Both of them alter the permeability of the cell membrane resulting in leakage of the cell contents.
- They are bactericidal.

Indications

1. Used topically for skin infections, ear and eye infections.
2. Oral colistin is used in children for diarrhea due to gram-negative bacilli.

Sodium Fusidate (Fusidic acid)

- They are bactericidal.
- *Fusidic acid*: It is steroid antibiotic which is active against gram (+ve) bacteria.
- On oral administration, it is readily absorbed and widely distributed.
- It acts by inhibiting protein synthesis and is mainly employed to treat penicillin resistant staphylococcal infections, specially osteomyelitis because it is concentrated in bones.
- It is available as ointment for skin infections.
- Gastrointestinal upsets, skin rashes, and jaundice may occur as adverse effects. It is given in doses of 50 mg per 8 hours.

Mupirocin

- Mupirocin is bactericidal against gram-positive and some gram-negative organisms.
- It is used as a 2% ointment for skin infections.

NEWER AGENTS**Linezolid**

- It is an oxazolidinone effective against gram-positive anaerobic organisms.
- It acts by inhibiting protein synthesis. It is orally effective.
- Linezolid is useful in the treatment of nosocomial infections resistant to other drugs.

Streptogramins

- It is a combination of **quinupristin** and **dalfopristin** in the ratio 30:70.
- It is bactericidal against gram-positive cocci including methicillin-resistant staphylococci.
- Given intravenously, streptogramins are rapidly metabolised and excreted largely through faeces. Therefore dose adjustment is not required in renal insufficiency.

Indications

The combination is used in the treatment of infections due to streptococci and methicillin-resistant staphylococci.

Adverse effects

It includes myalgia and pain at the site of infection.

Chemotherapy of Tuberculosis

TUBERCULOSIS AND MANAGEMENT

Definition

Tuberculosis is a chronic granulomatous inflammatory and infectious disease which is caused by *Mycobacterium tuberculosis* bacteria. Basically it is a disease of respiratory system but it can also affect other organ-system as well, i.e. GIT (Koch's abdomen)

- Tuberculosis is a major scourge of mankind with an estimated one-third of the world population currently infected. Each year more than 8 million persons are infected by *M. tuberculosis*
- It is also a major public health problem in developing countries like India.
- After massive spread of AIDS, the problem has become more complex, as tuberculosis and *Mycobacterium Avium Complex* (MAC) infections are more common and progressive in these patients.
- Although a large number of drugs are available for its treatment, there are certain problems also, viz.
 - If single drug is employed, drug resistant strains emerge rapidly. So 2, 3, or 4 drugs are used in combination.
 - Since organisms may lie dormant intracellularly for long period, drugs which cross cell membranes are used.
 - To treat tubercular meningitis, appropriate combinations of drugs are selected because all the drugs do not cross blood brain barrier.
 - Drug toxicity and patient compliance are also problems.
 - It is problematic to treat high, risk groups, contacts, HIV infected, etc.
 - However, with the advent of chemotherapy, tuberculosis once almost certainly fatal is now a curable disease.

Drugs Used in Tuberculosis

Based on antitubercular activity, drugs may be grouped as:

First line drugs

Rifampicin, Isoniazid, Pyrazinamide, Ethambutol, Streptomycin.

Second line drugs

Thiacetazone, Ethionamide, Para-aminosalicylic acid (PAS), Amikacin, Capreomycin, Cycloserine, Kanamycin, Ciprofloxacin, Rifabutin

Rifampicin (R) (rifampin):

- It is a highly effective semisynthetic derivative of one of the rifamycins, produced by *Streptomyces mediterranei*. It is bactericidal against sensitive organisms.
- It is bactericidal to *M. tuberculosis*, *M. leprae* and atypical mycobacterium.
- It also inhibits most gram-positive and gram-negative bacteria like *Staph. aureus*, *N. meningitidis*, *E. coli*, *Proteus* and *Pseudomonas*.

Pharmacokinetics

- Rifampicin is rapidly absorbed from guts and widely distributed in tissues and fluids including caseous material, cavities and cerebrospinal fluid.
- It is eliminated in bile and undergoes enterohepatic circulation. It is mainly excreted in feces and only a little amount is excreted in urine.
- It is a microsomal enzymatic **inducer**.

Antitubercular action

- Rifampicin is highly effective tuberculocidal agent.
- It acts on both intra- and extracellular organisms and is effective against tubercle bacilli resistant to other drugs.

- If given singly bacterial resistance develops either due to bacterial permeability barrier or to a mutation of DNA dependent RNA polymerase.

Mechanism of action

- Rifampicin binds to DNA dependent RNA polymerase and inhibits RNA synthesis in bacteria.
- It can also kill intracellular organisms by entering into phagocytic cells.

Adverse effects

- Nausea, vomiting, diarrhea and skin rashes are common side effects.
- In intermittent dosing regimen, a **flu-like syndrome** can occur.
- Hepatotoxicity and respiratory syndrome: breathlessness may occur.
- It may impart a harmless **orange-red color to urine sweat, tears and sputum**.
- It is contraindicated in hepatic dysfunction
- It induces microsomal enzymes. So it reduces the activity of several drugs, e.g. oral contraceptives, oral antidiabetics, warfarin, phenytoin, etc.

Therapeutic indications

It is effective against gram (+ve) and gram (-ve) cocci, gram (-ve) bacilli, *M. tuberculosis*, *M. leprae*, Chlamydia and Poxviruses. Its important uses are:

1. Tuberculosis: It is always used in combination with other antimycobacterial agents in a dose of 600 mg/ 24 hours orally.
2. Leprosy: It is used in combination with dapsone.
3. Other uses:
 - a. Meningococcal carriers: 600 mg twice a day for two days.
 - b. *H. influenzae* prophylaxis: 20 mg/kg/24 hours for 4 days.
4. Brucellosis: It is used in combination with doxycycline.
5. Systemic fungal infections: It is used to enhance the effect of amphotericin B.
6. To eradicate meningococcal carrier state

Isoniazid (INH-iso-Nicotinic Acid Hydrazide) (INH)

- Isoniazid is the most effective and cheapest primary antitubercular drug.
- It has structural resemblance with pyridoxine and nicotinic acid.
- It is bactericidal against actively growing (multiplying) tubercular bacilli, but static for resting bacilli.
- It is active in both acidic and alkaline medium

- It is effective against both intra-and extracellular organisms as INH destroys:
 - (i) Intracellular bacilli as it penetrates into the cells, i.e. tubercle bacilli in macrophages, and
 - (ii) Bacilli multiplying in the walls of the cavities.
- If used alone, mycobacteria develop resistance to it. Hence, it should be used in combination with other drugs.

Mechanism of action

- Isoniazid inhibits the synthesis of mycolic acids which is an important component of the mycobacterial cell wall. INH also has effect on nucleic acid.

Pharmacokinetics

- On oral administration, it is readily absorbed from gut and is well distributed in body fluids, all tissues, tubercular cavities, necrotic tissues and CSF.
- It is metabolized in liver by **acetylation**. The activity of acetyl transferase enzyme is genetically determined. So the blood levels of isoniazid depend on the rate of acetylation.
- In 'slow acetylators', neurotoxicity is more while in 'rapid acetylators' hepatotoxicity is more. It is excreted in urine partly in free form and partly in the form of metabolite.

Adverse effects

- It may cause neurotoxicity, hepatotoxicity and allergic reactions.
- **Hepatitis** is a major adverse effect, more common in alcoholics.
- **Peripheral neuritis** (due to interference with utilization and increased excretion of pyridoxine) can be avoided by giving prophylactic pyridoxine (20-50 mg daily with INH).
- It can cause CNS toxicity including **psychosis and seizures**, but are less common.
- Other minor effects like anorexia, GI discomfort and allergic reactions can occur.
- It should be employed with care in presence of liver and kidney disease, epilepsy, alcoholism and to breastfeeding mothers.
- Systemic Lupous Erythematosus like syndrome.

Dose – 300 mg per 24 hours; in children 10 mg per kg per 24 hours; for chemoprophylaxis, it is given alone in dose of 300 mg per 24 hours for one year.

Pyrazinamide (Z)

It is a synthetic derivative of nicotinic acid. It is a bactericidal drug. It is particularly useful in **tuberculosis-**

meningitis because of good meningeal penetration. It is tuberculocidal, being more active in acidic pH.

- Pharmacokinetics: On oral administration, it is well absorbed and widely distributed in tissues including macrophages and CSF. It is excreted in urine
- Mechanism of action is not known. It is effective against intracellular bacilli.
- If it is used alone, resistance develops.
- **Hepatotoxicity** is the most common adverse effect. Hyperuricemia (due to - excretion of uric acid), arthralgia, anorexia, vomiting and rashes may be seen.

It is given in doses of 20-30 mg per kg daily.

Ethambutol

It is synthetic tuberculostatic drug.

- On oral administration, about 75-80% of the drug is absorbed and widely distributed in tissues and fluids including CSF. Partly it is metabolized. It is excreted in urine.
- It acts on fast multiplying bacilli in the cavities. It is employed in the treatment of tuberculosis in combination with other antitubercular drugs.
- It is also effective against atypical mycobacterium. It inhibits the incorporation of mycolic acids into the mycobacterial cell wall.
- Adverse effects include nausea, anorexia, headache, and fever. It may increase blood urate concentration due to reduced uric acid excretion.
- **Optic neuritis** and retinal damage resulting in visual acuity and inability to differentiate red color from green color is an important adverse effect which needs withdrawal of the drug.
- Other adverse effects are mental disturbances and rarely allergic reactions. It should be avoided in very young kids and elderly patients.
- If it is used alone, bacterial resistance emerges rapidly.

Recommended adult dose is 15 mg per kg, given once a day.

Streptomycin

It is an aminoglycoside. It has already been discussed in detail. It is tuberculocidal, acts only against extracellular organisms due to poor penetrating power.

- It has to be given IM. When used alone resistance develops.
- Because of these disadvantages and its toxicity [ototoxicity and nephrotoxicity], streptomycin is the least preferred for the first line drugs.
- Its limitations are:
 - Parental administration
 - Nonpenetration into cells (macrophages) and CSF

- Toxicity
- Development of bacterial resistance.

Therefore, at present, it is kept reserved in the main line drugs.

Thiacetazone

- It is tuberculostatic with low efficacy; it delays the development of resistance to other drugs and its low cost makes it a suitable drug in combination regimens.
- Hepatotoxicity, dermatitis, allergic reactions and GI side effects may occur.

Ethionamide

- It is structurally similar to isoniazid.
- Ethionamide is a secondary agent used only when primary drugs are ineffective.
- This tuberculostatic drug is effective against both intra- and extracellular organisms. It is also effective in atypical mycobacteria.
- Anorexia, nausea, vomiting and metallic taste in the mouth are the most common adverse effects.
- It can also cause hepatitis, skin rashes and peripheral neuritis (needs prophylactic pyridoxine).

It is administered orally up to 1 gm daily in divided doses.

Recommended daily doses of antitubercular drugs

Drugs	Doses
Isoniazid (INH)	300-400 mg
Ethambutol (E)	800-1000 mg
Rifampicin (R)	450-600 mg
Streptomycin (S)	750-1000 mg
Pyrazinamide (Z)	1200-1500 mg
Thiacetazone (T)	150 mg

Para-amino Salicylic Acid (PAS)

- It is related to sulfonamides and is tuberculostatic.
 - It is a synthetic drug. Its sodium salt is readily absorbed on oral administration and widely distributed in body fluids
 - Gastrointestinal effects like nausea, anorexia, epigastric pain and diarrhea make it a poorly tolerated drug.
 - Allergic reactions and hepatitis are also seen. It is rarely used.
 - It has two main disadvantages, i.e. weak bacteriostatic activity and a very high dose (8-12 gm per 24 hours).
- After discovery of rifampicin and many other antitubercular drugs, it is now obsolete.

Other Second Line Drugs**Kanamycin, Amikacin, Viomycin and Capreomycin**

- They are second line drugs that need parenteral administration
- First two are amino glycosides while last two are peptides.
- All of them have similar **pharmacokinetics** and adverse effects. Since not absorbed on oral administration, they are given IV. They are excreted in urine. They do not cross blood-brain barrier.
- All of them cause ototoxicity and nephrotoxicity.
- Cross resistance exist among each other but not against main line drugs except streptomycin.
- The importance of amikacin has increased with multidrug resistance cases because most of the drug resistant strains are susceptible to amikacin. Amikacin is also effective against atypical mycobacteria.
- Cross resistance is not seen between streptomycin and amikacin. However, it must be used with other antitubercular drugs.

They are given IM in a dose of 1 gm daily except viomycin which is given in a dose of 2 gm twice daily.

Cycloserine

- It is a structural analogue of D-alanine.
- It acts by inhibiting bacterial cell wall synthesis by competing with D-alanine.
- It is tuberculostatic and is also effective against some gram-positive organisms.
- It is used only in resistant tuberculosis.
- **Adverse effects:** It may produce vertigo, tremors, and convulsions.
- It causes CNS toxicity including psychosis. Pyridoxine (150 mg per day) is administered to prevent occurrence

of peripheral neuropathy and central nervous system side effects.

- It is contraindicated in epilepsy, depression and anxiety.

It is given in a dose of 250 gm twice daily.

Fluoroquinolones

- Ciprofloxacin, ofloxacin and sparflaxacin and levofloxacin are specially effective. They inhibit tubercle bacilli and atypical mycobacteria.
- These drugs are used in combination with other drugs such as pyrazinamide in multi-drug resistant tuberculosis.
- Ciprofloxacin is given in a dose of 750 mg twice daily while levofloxacin is used in a dose of 500 mg once a day.

Rifabutin (Ansamycin)

- It is a derivative of rifampicin and its activity is also similar to rifampicin.
- Cross resistance exists between the two drugs.
- It is used to treat atypical mycobacterial infection. It is a preferred drug where HIV infection coexists. It is administered in a dose of 300 mg per day.

TREATMENT OF TUBERCULOSIS (Fig. 12.10.1)

- Treating tuberculosis is one of the most difficult strategies.
- This is because of some characteristic properties of *Mycobacterium tuberculosis* like slow division, development of resistance, ability to remain as dormant for years and intracellular location of the bacilli are the main problems in its treatment.
- Moreover, the caseous material (pus) makes it difficult for the drugs to reach up to the bacteria.

Antitubercular actions and characteristic adverse effects of some antitubercular drugs

Drug	Antitubercular action	Serious toxicity
Isoniazid	Tuberculocidal; acts on intra and extracellular organisms	Peripheral neuritis, seizures, psychosis
Rifampicin	Tuberculocidal; Acts on intra and extracellular organisms, persists and drug resistant organisms	Hepatotoxicity, flu-like syndrome, neuritis; urine and secretions are colored orange-red
Pyrazinamide	Tuberculocidal, kills intracellular organisms; more active in acidic pH	Hepatotoxicity, arthralgia, hyperuricemia
Streptomycin	Tuberculocidal, acts on extracellular organisms	Ototoxicity, nephrotoxicity
Ethambutol	Tuberculostatic; inhibits tubercle bacilli in the walls of cavities	Optic neuritis with visual acuity and red-green color blindness
Thiacetazone	Tuberculostatic low efficacy. Delays development of resistance to other drugs	Hepatotoxicity dermatitis

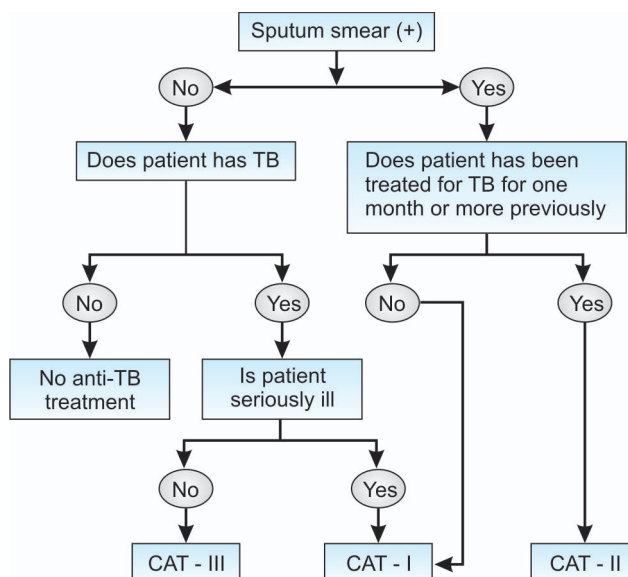


Fig. 12.10.1: Optimum regimens according to RNTCP (Revised) National TB Control Program

- The need for long-term treatment, drug toxicity, cost and thereby poor patient compliance has all added to further complicate the problem.
- But with the availability of effective drugs, most patients can now be treated as out patients.

The aim of treatment is to kill the dividing bacilli thus making the patient sputum negative and to destroy the

parasites in order to prevent relapse and ensure complete cure (Tables 12.10.1 and 12.10.2).

A combination of drugs is used in tuberculosis to:

1. Delay the development of resistance
2. Reduce toxicity
3. Shorten the course of treatment because failure rates are high and compliance is poor.

Table 12.10.1: Different category-wise treatment regimens

	Initial phase	Constant phase	Total duration
CAT-I New cases sputum (+) Seriously ill patients (-) Seriously ill (extra Pulmonary eg. meningitis)	2 HRZE/(S) or 2 H₃R₃Z₃E₃*	4 HR 4 H₃R₃*	6 Months
CAT-II Sputum (+) Relapse Sputum (+) Failure Sputum (+) Default Very seriously ill Patient or complex/ Resistance case	2 HRZES → or 2H₃R₃Z₃E₃S₃* →	1 HRZE → 5 HRE 1 H₃R₃Z₃E₃* → 5 H₃R₃E₃*	8 Months
CAT-III Sputum (-) Not seriously ill Pregnancy AIDS	2HRZ or 2 H₃R₃Z₃*	4 HR 4 H₃R₃*	6 Months

Where: **S** = Streptomycin, **R** = Rifampicin, **H** = Isoniazide, **Z** = Pyrazinamide
E = Ethambutol, **T** = Thiacetazone, **PAS** = Para-amino Salicylic Acid.
 [CAT-I, II and III are 3 different categories of the patients]

Table 12.10.2: Category-wise alternative treatment regimens for tuberculosis (WHO-1999)

I	2 HRZE (S)	4 HR/4H ₃ R ₃ or 6 HE	6 8
II	2 HRZES + 1 HRZE	5 HRE or 5 H ₃ R ₃ E ₃	8 8
III	2 HRZ	4 HR/4H ₃ R ₃ or 6 HE	6 8
IV	MDR and Chronic Case (Smear + after complete t/t)	*	

* For H resistance:– RZE for 12 months

For H + R resistance: ZE + S/Kmc/Am/Cpr/of could be used.

Resistant tuberculosis

- If sputum remains positive even after 6 months of treatment, organisms are likely to be resistant.
- Such patients should be treated with 4-5 drugs, of which 3 should be of first line drugs and treatment is continued for at least 8 months to 1 year after the sputum becomes negative.
- Treatment under CAT-II

Role of glucocorticoids

- As steroids depress host defense mechanisms, they should be used only in conditions like tubercular meningitis, miliary tuberculosis, pleural effusion, renal tuberculosis and rapidly progressing pulmonary tuberculosis.
- Steroids suppress inflammatory reaction which can lead to extensive fibrosis and damage.

Chemoprophylaxis

It is given only in:

- Contacts of open cases especially in children

- Patients with old inactive disease who have not been adequately treated.
- INH is used daily (5 mg/kg) for 6-12 months.

Tuberculosis in AIDS patients

Due to depressed immunity, AIDS patients are likely to have more severe and rapidly progressing tuberculosis. Adverse effects to antitubercular drugs are more common in them. They should be given INH + R + S + Z for 2 month followed by INH + R for 7 months.

Drugs for mycobacterium avium complex (MAC)

- Infection with MAC is more common in HIV patients.
- The drugs effective are *rifabutin*, *clarithromycin*, *azithrocylin*, *fluoroquinolones*, *ethambutol*, *clofazimine*, *amikacin* and *ethionamide*. *Clarithromycin* + *ethambutol* is the preferred regimen for MAC infection and needs life long treatment.
- Rifabutin is used for prophylaxis.

Chemotherapy of Leprosy

CHEMOTHERAPY OF LEPROSY

Leprosy is caused by *Mycobacterium leprae*: It is a chronic infectious disease affecting skin, mucous membranes and nerves. In India leprosy (kustha roga) is a major public health problem affecting millions of people.

- Hansen discovered lepra bacillus in 1873. As lepra bacillus does not grow on artificial media and cannot be transmitted to all animals, it is difficult to culture this organism and study the effect of drugs.

There are two major types:

- **Lepromatous leprosy (Multibacilliary type)** with extensive involvement. Lepromine reaction is negative.
- **Tuberculoid leprosy (Paucibacilliary type)** with single or few skin lesions and neurological involvement. Lepromine reaction is positive.
- Dimorphic (borderline) and indeterminate are other types of leprosy.
- It is a chronic disease and its treatment is very long (even it has to be life long). In India, leprosy was being treated with chaulmoogra oil / hydrocarpus oil for centuries. But for the last 50 years, these oils are no more used because of the advent of antilepra chemotherapy.

The main antileprotic drugs are:

Drugs used in leprosy

- Sulfones: Dapsone
- Rifampicin
- Clofazimine
- Ethionamide.

Dapsone

It is diamino-diphenyl-sulfone (DDS) and is related to sulfonamides.

Mechanism of action

Like sulfonamides, It acts by inhibiting folate synthesis by competing with PABA (it inhibits the incorporation of PABA into folic acid).

Pharmacokinetics

- Dapsone is slowly but completely absorbed from gut and widely distributed in the body. It reaches in high concentrations in skin.
- It is metabolized, i.e. it is acetylated as well as undergoes glucuronide and sulphate conjugation in liver.
- It is excreted in urine as conjugated metabolites. It undergoes entero-hepatic circulation also.

Actions

- Dapsone is leprostatic. Though it inhibits growth of many other bacteria, the dose needed is high and is therefore not used in other infections.
- The lepra bacillus develops resistance to dapsone on prolonged use. To avoid development of bacterial resistance, it is used in combination with rifampicin.
- Its other use is to treat chloroquine resistant malaria in combination with pyrimethamine.

Adverse effects

- Dapsone is well-tolerated—anorexia, nausea and vomiting are common side effects.
- Fever, pruritus, rashes and dermatitis can occur.
- Hemolytic anemia is the most important dose-related toxicity (more common in patients with G6PD deficiency). Its due to intravascular hemolysis
- It may induce peripheral neuropathy, hepatitis, allergic skin reactions and psychosis.
- Hepatitis and agranulocytosis are seen.
- Patients with lepromatous leprosy, may develop or precipitate lepra reactions (erythema nodosum leprosum) which are of two types and may be suppressed by corticosteroids or by clofazimine.

Rifampicin

- It is rapidly bactericidal to *M. leprae* and is highly effective.
- It can be conveniently given once monthly.
- It rapidly makes leprosy patients noncontagious. However, it should not be used alone because some bacilli persist even after prolonged treatment and become resistant to the drug.
- Used in combination with dapsone, it shortens the duration of treatment.

Clofazimine

- It is phenazine derivative (a dye). It has leprostatic and anti-inflammatory properties.
- Its absorption from gut is variable. It is stored in reticuloendothelial tissues and skin. It is released from these sites very slowly and excreted in urine and bile.
- It probably produces its effect by interfering with template functions of DNA. It is used in patients who are resistant to sulphones.
- Since it has anti-inflammatory property, it is useful in preventing the development of erythema nodosum leprosum.
- It is also used in combination therapy to treat atypical mycobacterial infection caused by *M. avium* specially in patients of AIDS.
- It is given in a dose of 100-300 mg daily by oral route. Treatment may continue for one year.
- It may cause gastrointestinal upsets and red-brown to nearly black discoloration of skin especially on the exposed parts which remains for several months. It can also cause dryness of skin, itching and photo toxicity.
- Clofazimine should be avoided during early pregnancy and in patients with liver and kidney damage.

Other antilepra drugs: These are used only as alternative drugs in multiple drug therapy regimens. These drugs are:

- **Ofloxacin:** It is fluoroquinolone. It is highly active against *M. leprae*. It is used as a component of multidrug regimen in case of rifampicin cannot be used or to shorten the duration of therapy. It is given in doses of 400 mg per day orally.
- **Minocycline:** It is tetracycline. Being highly lipophilic, it is active against *M. leprae*. It is used as an alternative in multidrug therapy regimens. It is given in doses of 100 mg per day orally.
- **Clarithromycin:** It is a macrolide antibiotic which has significant activity against *M. leprae*. It is used as an alternative in multidrug therapy regimens. It is given orally in doses of 500 mg per day.
- **Ethionamide:** It has significant antileprotic activity. However, it should be used only when absolutely necessary because it causes hepatotoxicity in 10% patients.

TREATMENT OF LEPROSY

WHO has recommended a combination of drugs in leprosy to:

1. Eliminate bacteria
2. Prevent drug resistance
3. Reduce the duration of therapy.

Different drugs and doses used for the treatment of leprosy

Drugs	Doses
Dapsone	100 mg/day
Clofazimine	50 mg/day or 300 mg/monthly
Rifampicin	600 mg once in a month.
Ofloxacin	400 mg/day
Minocycline	100 mg/day
Clarithromycin	500 mg/day

Multi-drug regimen

Drugs	Multibacillary leprosy (for 24 months)	Paucibacillary leprosy (for 6 months)
Rifampicin	600 mg once a month supervised	600 mg once month supervised
Dapsone	300 mg daily self-administered	100 mg daily self-administered
Clofazimine	300 mg once monthly supervised	—
	50 mg daily self-administered	—

All drugs are given orally

Other regimen

Total 3 main drugs	+ Two alternative drugs
1. Dapsone	* Ofloxacin
2. Clofazimine	* Minocycline or
3. Rifampicin	* Clarithromycin

Lepra reactions

These reactions are the acute exacerbations that occur in leprosy. They are triggered by acute infections, stress, anxiety and treatment with dapsone.

- **Type I reactions** seen in tuberculoid leprosy is a delayed hypersensitivity reaction to the antigens of *M. leprae*.

- Cutaneous ulcerations occur and existing lesions show more erythema.
- It is treated with corticosteroids or clofazimine.
- **Type II reactions** are seen in lepromatous leprosy (are known as erythema nodosum leprosum ENL).
 - New lesions appear and the existing lesions become worse. Fever, lymphadenitis and neuralgia may occur. It is a hypersensitivity reaction to the antigens of *M. leprae*.
 - Type II reactions can be treated with **clofazimine** which is effective due to its anti-inflammatory properties. **Chloroquine, corticosteroids or thalidomide** are also effective.
 - Dapsone should be continued throughout.

Antiviral Drugs

Bacterial infections can be satisfactorily controlled by chemotherapeutic agents, but it is difficult to control viral infections because:

- They have no cell wall.
- They are not associated with enzyme system
- They are obligate intracellular parasites that require the active participation of the metabolic processes of the invaded cell to survive, i.e. depends upon the host cells for their food, growth and multiplication.

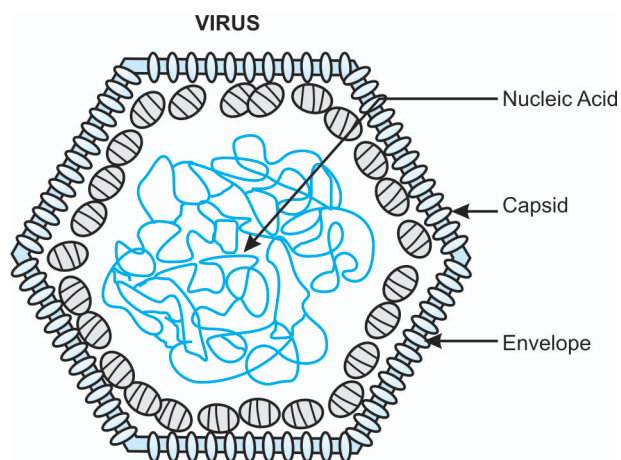


Fig. 12.12.1: Structure of virus

The virus attaches itself to the host cell membrane, penetrates it, DNA/RNA is released in the host cell where it is duplicated. The viral components are assembled and the mature viral particles are then released from the host cell.

Chemotherapy can interfere with any of these steps. But drugs that interfere with viral replication may also interfere with host cell functions.

A virus is made up of nucleic acid (protein) enclosed in a protein core called as **Capsid** (Fig. 12.12.1).

They are of two types:

- **DNA Viruses:** H_3V : Herpes Simplex, Hepatitis B and Human Cytomegalo Virus, [Varicella Zoster].
- **RNA Viruses**
 - a. RRM: Rubella, Rabies and Measles Viruses
 - b. PYD: Poliomyelitis, Yellow fever, and Dangeue Viruses
 - c. HIV: Human Immunodeficiency Virus

CLASSIFICATION

1. Anti-herpes viral agents

Acyclovir, Gancyclovir, Idoxuridine, Trifluridine, Vidarabine, Foscarnet

2. Anti-retroviral agents

a. Reverse transcriptase inhibitors (NRTI)

Zidovudine, Didanosine, Zalcitabine, Stavudine.

b. NNRTI

Nevirapine, Efavirenz

c. Protease inhibitors

Indinavir, Ritonavir, Saquinavir, Nelfinavir

3. Anti-influenza viral agents

Amantadine, Rimantadine

4. Others

Ribavirin, Interferons

ANTI-HERPES VIRAL AGENTS

Acyclovir. It is quite effective against Herpes simplex virus (HSV) type 1 and type 2, Varicella zoster virus (VZV) and Epstein-Barr virus (EBV).

Chemistry: Acyclovir is a synthetic purine nucleoside analog with an acyclic side chain.

Mechanism of action: It is taken up by the virus infected cell, converted to acyclovir triphosphate and this inhibits viral DNA synthesis by two mechanisms

1. It interferes with viral DNA polymerase and

2. It is incorporated into DNA and leads to premature chain termination.

The drug is several hundred times more toxic for the herpes viruses than for mammalian cells because of the enhanced affinity of the viral enzyme thymidine kinase for acyclovir.

Pharmacokinetics

- Oral absorption of acyclovir is poor; only 20% get absorbed.
- It is well distributed—attains good concentration in the CSF and aqueous humor.
- Excreted unchanged in urine via both glomerular filtration and tubular secretion.
- $T_{1/2} = 2-3$ hours.

Adverse effects: Orally, acyclovir is well tolerated; however, nausea, vomiting, diarrhea, rashes and headache can occur occasionally.

Given IV, Intravenous therapy can cause crystalline nephropathy, neurological reactions, local phlebitis and rashes. Encephalopathy develops only in 1% of patients.

Topical applications can cause local discomfort burning sensation and pain.

Uses

1. **Herper zoster:** Acyclovir shortens the duration of illness. In immunodeficient patients—IV acyclovir is used.
2. **HSV (Herpes Simplex Virus) infections:** Infection with HSV-1 causes diseases of the mouth, face, skin, esophagus or brain. HSV-2 usually causes infections of the genitalia, rectum, skin, hands or meninges:
 - Oral acyclovir is effective in primary and recurrent genital and labial herpes. In mild cases, topical acyclovir can be tried. In recurring genital herpes—oral acyclovir is given for 1 year.
 - HSV encephalitis and other severe HSV infections: i.e. Acyclovir is the drug of choice.
 - HSV keratoconjunctivitis: Acyclovir eye drops are effective.
3. **Chickenpox:** In adults and in immunodeficient patients, acyclovir reduces duration and severity of illness. In children, routine use is not recommended.

Idoxuridine: It is basically effective in DNA viruses only

Chemistry: It is 5-iodo-2 deoxy-uridine, (IUDR) a **Thymidine analogue**.

Mechanism of action: It competes with thymidine and gets incorporated into DNA – leads to formation of wrong (faulty) DNA [therefore viral components are manufactured but they are non-virulent] even there occurs wrong viral protein synthesis.

Uses: Idoxuridin is used topically in HSV type 2 infection of eye, i.e. **Kerato conjunctivitis** (it is too toxic for systemic use).

Adverse effect: Eyelid edema, itching, allergic reactions may occur.

Bone marrow toxicity on (IV inj.) is an important toxicity.

Ganciclovir

Chemistry: Ganciclovir is a synthetic nucleoside analogue of 2'-deoxyguanosine.

Mechanism of action: Ganciclovir inhibits viral DNA synthesis in the same manner as that of acyclovir.

Pharmacological effects

- Ganciclovir inhibits replication of herpes simplex virus types 1 and 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus.
- Ganciclovir is more active against cytomegalovirus, in vitro, than acyclovir, but resistant strains can develop.

Therapeutic uses: Ganciclovir is indicated for the treatment of cytomegalovirus retinitis in immunocompromised individuals, including patients with AIDS. However, relapse is common, even with continuous treatment.

Adverse effects

- When administered intramuscularly or subcutaneously, ganciclovir may cause severe tissue irritation.
- Granulocytopenia occurs in 40% and thrombocytopenia in 20% of treated patients. These are generally reversible on discontinuation of treatment.
- CNS effects, from headache to psychosis, convulsions, or coma, can occur in 5%-15% of patients.
- Anemia, fever, rash and abnormal liver function values can occur.
- Ganciclovir is teratogenic and mutagenic in animals.

Trifluridine: It is used topically in HSV eye infections.

Chemistry: Trifluridine is a fluorinated pyrimidine nucleoside.

Mechanism of action: Trifluridine inhibits DNA synthesis but its specific mechanism of action is unknown.

Pharmacological effects

- Trifluridine is active against herpes simplex virus types 1 and 2 and vacciniavirus.
- Some strains of adenovirus are also inhibited.

Therapeutic use: Trifluridine is indicated for the treatment of primary *keratoconjunctivitis* and *recurrent epithelial keratitis* resulting from herpes simplex virus types 1 and 2.

Preparations and administration: Trifluridine is administered as an ophthalmic solution into the cornea of the affected eye.

Adverse effects: Include transient burning and stinging and palpebral edema.

Foscarnet: It is given intravenously to treat CMV retinitis as an alternative to ganciclovir.

Chemistry: Foscarnet is phosphonoformic acid.

Mechanism of action: Foscarnet inhibits DNA polymerase of human herpes viruses and the reverse transcriptase of HIV at a different site from other nucleoside analogues (e.g. acyclovir, ganciclovir, zidovudine).

Therapeutic uses

- Foscarnet is the drug of choice for acyclovir-resistant herpes simplex virus and varicella-zoster virus infections.
- Foscarnet is used to treat cytomegalovirus retinitis in AIDS patients, especially in the case of ganciclovir-resistant cytomegalovirus.

Preparations and administration: Foscarnet is available for the intravenous treatment of cytomegalovirus retinitis in AIDS patients.

Adverse effects

- Foscarnet is less well tolerated than ganciclovir; however, it causes less myelosuppression.
- Foscarnet binds divalent metal ions, resulting in metabolic abnormalities.
- Dose-limiting nephrotoxicity is common.

Famciclovir: It has good oral bioavailability and prolong $t_{1/2}$. It inhibits HSV and VZV infections but not acyclovir resistant strains. Some activity against HBV (hepatitis B Virus) has been noted. Adverse effects includes; headache, nausea, diarrhea, rashes, etc.

Vidarabine: It was used earlier for HSV and VZV infection but is now replaced by acyclovir.

Valacyclovir: It is a prodrug of acyclovir. Famciclovir is a prodrug of penciclovir—used in HSV and VZV infections discussed above.

AGENTS USED FOR THE TREATMENT OF AIDS AND RELATED OPPORTUNISTIC INFECTIONS

- AIDS is caused by HIV, a retrovirus and member of the lentivirus family. Two subtypes, HIV-1 and HIV-2, have been recovered from patients with AIDS.
- A large number of human cells can be infected by HIV, including macrophages and glial cells. However,

the virus preferentially replicates in CD4+ helper T lymphocytes.

- The agents used are described below:

ANTI-RETROVIRAL AGENTS

These are the drugs used for the treatment of HIV and AIDS related complex, where it may increase the life expectancy, and decreases the complications but does not cure the infection.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS [NRTI]

Zidovudine (Azido-thymidine, AZT)

Chemistry: Zidovudine is a synthetic thymidine analogue.

Mechanism of action

- Zidovudine, as the triphosphate, inhibits the DNA polymerase (reverse transcriptase) of HIV.
- HIV reverse transcriptase is 100 times more susceptible to inhibition by zidovudine than is the DNA polymerase of mammalian cells.
- Zidovudine triphosphate is incorporated into viral DNA and terminates chain growth during DNA synthesis.

Pharmacokinetics

- Zidovudine is well absorbed from the gastrointestinal tract.
- It is rapidly cleared from the blood ($T_{1/2} = 1$ hour), metabolized in the liver, and excreted in urine.
- Zidovudine penetrates readily into the cerebrospinal fluid.

Resistance: With continued use, resistance develops which is due to point mutation and is associated with clinical deterioration. If AZT is used alone, approx. 50% of the recipients shows resistance and non response to AZT.

Therapeutic uses

- Zidovudine increases median survival from less than 9 months to more than 2 years after diagnosis of AIDS.
- Its use in symptomatic HIV-infected patients slows progression to AIDS and prolongs survival.
- Its use in asymptomatic HIV-infected patients may slow progression to the symptomatic condition, but does not impact survival.
- Given during pregnancy and continued in new born for 6 weeks AZT reduces the risk of transmission to the baby. But it has no prophylactic value in those who are accidentally exposed to HIV infection (e.g. following blood transfusion). Combination therapy of AZT with didanosine or zalcitabine gives better results.

Preparations and administration: Zidovudine is administered orally every 4 hours around the clock. When anemia develops, therapy is either interrupted or the dose is reduced, or the hematocrit is maintained with transfusions.

Adverse effects

Hematological toxicity: Administration of erythropoietin and granulocyte-macrophage colony stimulating factor (GM-CSF) may help alleviate the hematological effects.

- Severe anemia, and neutropenia are the important dose related adverse effects.
- Neutropenia is very common, especially in patients with AIDS.
- Anemia, granulocytopenia, and thrombocytopenia are usually reversible when the dosage is decreased or the drug is stopped.

Neurotoxicity

- Severe headaches and insomnia are common but are less severe after the first week of therapy.
- Seizures and wernicke's encephalopathy have been reported.

Other adverse effects: Nausea and myalgias occur often at the start of therapy.

Drug interactions

- Ribavirin interferes with the antiviral effect of zidovudine.
- Probenecid slows the metabolism and excretion of zidovudine.
- Acetaminophen (PCM) interferes with glucuronidation of zidovudine in the liver and increases AZT toxicity.

Didanosine (dideoxyinosine)

Mechanism of action: Didanosine is a reverse transcriptase inhibitor.

Therapeutic use: Sequential use of zidovudine and didanosine, rather than continuing zidovudine, appears to delay clinical deterioration.

Adverse effects include:

1. Acute pancreatitis, hepatic failure
2. Painful peripheral neuropathy
3. Development of *in vitro* resistance

Zalcitabine (dideoxycytidine)

Mechanism of action: Zalcitabine is a reverse transcriptase inhibitor.

Therapeutic use: Zalcitabine can be used concurrently with zidovudine in patients with advanced HIV infection.

Adverse effect: Peripheral neuropathy can limit dosage.

Stavudine

- It is a thymidine analogue
- Its mechanism of action is same as that of AZT, therefore stavudine antagonizes AZT or vice versa
- **Resistance** develops, on long-term use, because of point mutation.
- **Pharmacokinetics:** Absorption is good
 $t_{1/2} = 1.5$ hours
- **Adverse effect:** Peripheral neuropathy, but pancreatitis is rare.

Use: Used in AIDS treatment in combination with other drugs.

Lamivudine: (dideoxycytidine analogue)

It gets phosphorylated intracellularly to (Lamivudine triphosphate) which inhibit:

- Hepatitis B virus, DNA polymerase and
- HIV reverse transcriptase

Mechanism of action: Incorporated into DNA and results into chain termination.

Most human DNA are not affected, that's why systemic toxicity of lamivudine is very less.

Resistance: Resistance also develops, slowly and is due to point mutation. Cross-resistance is also found.

Pharmacokinetics

- Bioavailability is very high
- Plasma half life is 6 to 9 hours. Half life of Intracellular triphosphate metabolite is > 12 hours.
- Excretion is mainly through kidney via (urine) and in unchanged form.

Use: In the treatment of AIDS and Chronic Hepatitis B infection. Viremia return after 1 year of treatment therefore interferon therapy as an adjuvant is effective.

Adverse effect

- Headache, fatigue, nausea, anorexia, abdominal pain
- Rarely: Pancreatitis, neuropathy
- Hematological adverse effect does not occur.

Abacavir (ABC)

- Guanosine alalogue and a potent ARV drug. Resistance develops slowly, bioavailability is 80%. Hypersensitivity is the main problem.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR [NNRTI]

Nevirapine and Efavirenz

Mechanism of action: They directly inhibit HIV reverse transcriptase enzyme

- No incorporation with DNA
- No intracellular phosphorylation.

Potency is higher than AZT in HIV 1 but lesser than AZT in HIV 2.

Resistance is there and is due to point mutation.

Pharmacokinetics

- Absorption: Good
- Metabolized in Liver
- $t_{1/2} = 30$ hrs.
- Efavirenz has incomplete oral absorption, but $t_{1/2}$ is greater than 48 hours.
- They induces [Cyt. P450] therefore they have higher metabolism of their own and other drugs.

Use: In combination therapy for the treatment of AIDS.

Adverse Effect: Rash/Headache/Neuro-psychiatric disorders

RETROVIRAL PROTEASE INHIBITORS

Ritonavir, Indinavir, Nelfinavir are available in India

Aspartic Protease Enzyme: It is required for the production of structural proteins and enzymes of viruses.

Mechanism of action: Protease inhibitor act by inhibiting Protease Enzymes, which ultimately inhibit the synthesis of viral structural proteins and various enzymes (reverse transcriptase).

It act at the late step in HIV replication therefore effective in newly (freshly) + chronically infected cells.

- Potency of RPI is > than AZT

Pharmacokinetics

- Oral bioavailability: Variable
- $T_{1/2} = 2-5$ hours.
- Metabolized by – Cyt. P3A4 (induces its own metabolism)
- Monotherapy with protease inhibitors, reduces HIV viral levels and increases CD4 counts
- But resistance develops, therefore they are used in combination therapy only in the treatment of AIDS.

Adverse effect

- GI intolerance, discomfort, headache and dizziness
- Abnormal fat distribution
- Higher incidences of urinary calculi.

ANTI-INFLUENZA VIRAL AGENTS

Amantadine and Rimantadine: It inhibit the replication of influenza A viruses.

Chemistry

- Amantadine is a synthetic tricyclic amine with a structure unrelated to that of any other antimicrobial agent.
- Rimantadine is the α -methyl derivative of amantadine.

Mechanism of action

- Amantadine and rimantadine may block or prevent: the uncoating (early step of viral replication)
 - Interferes with the primary transcription of viral RNA.
- Interferes with penetration of viruses.
- Also interferes with assembling of viruses.
- Both drug are inactive against influenza B.
- Rimantadine is more potent drug out of two.

Pharmacokinetics

- Amantadine is completely absorbed from the gastrointestinal tract and is not metabolized. It is excreted through the kidney via (urine) in unchanged form. $T_{1/2}$ is long = 16 hours.
- Oral bioavailability of rimantadine is high and cross resistance is also present
- Rimantadine is well absorbed and also extensively metabolized. Its plasma half-life is also double to that of amantadine.

Therapeutic uses

Antiviral use

- The major anti-infective use for amantadine and rimantadine is for prophylaxis during influenza A virus epidemics. Unvaccinated patients of all ages who are at high risk are advised to receive one of these drugs.
 - Both drugs do not alter the immune response to influenza; thus, vaccination can be given concurrently with the drug.
 - Both drugs can help to protect immunodeficient patients and those on dialysis, who may have a poor antibody response to the vaccine.
- Amantadine and rimantadine may also be useful in shortening the duration of symptoms when administered after the onset of illness.
- The use of amantadine in parkinsonism is also very important, where; amantadine enhances the release of dopamine and is beneficial in the treatment (Table 12.12.1).

Preparations and administration: Amantadine and rimantadine are administered orally.

Table 12.12.1: Indications of some commonly used antiviral drugs

Drugs	Routes	Indications
Acyclovir	Topical	Herpes genitalis, HSV eye infections
	Oral	Herpes genitalis/mucocutaneous HSV chickenpox
	IV	HSV encephalitis, severe herpes genitalis, chickenpox/herpes zoster in immunocompromized patients
Idoxuridine, Trifluridine	Topical	HSV keratitis
Ganciclovir	IV/oral	CMV infections
Foscarnet	IV	CMV retinitis, acyclovir resistant HSV infections
Amantadine	IV	Influenza A
Rimantadine, Ribavirin	Aerosol oral /IV	RSV bronchiolitis, severe influenza and measles
α -Interferon	IV	Chronic hepatitis B and C, genital warts, Kaposi's sarcoma
Zidovudine	Oral	HIV infection

Adverse effects: Amantadine causes dose-related CNS effects (e.g. confusion, hallucinations, seizures anorexia, delirium, ataxia, convulsion and coma). Rimantadine has a low risk of CNS effects; however, patients with psychiatric disorders or a history of epilepsy require close monitoring when receiving amantadine or rimantadine.

OTHER ANTIVIRAL AGENTS

USED FOR TREATMENT OF VIRAL INFECTIONS

Ribavirin (Tribavirin)

Chemistry: Ribavirin is a synthetic purine nucleoside analog.

- It has broad spectrum antiviral activity.

Mechanism of action: This appears to be multiple:

- Ribavirin monophosphate inhibits enzymes needed for the synthesis of guanine nucleotides.
- Ribavirin triphosphate inhibits viral RNA polymerase by competing for substrate sites.
- The triphosphate also interferes with the formation of viral messenger RNA.

Pharmacological effects: Ribavirin is active *in vitro* against several DNA and RNA viruses, including herpes simplex, influenza A and B, and respiratory syncytial virus (RSV). High concentrations inhibit replication of the viruses.

Therapeutic uses and administration

- Ribavirin in aerosol form decreases morbidity due to severe RSV infection in infants and young children. It must be administered with using specific small-particle aerosol generator.

- Intravenous ribavirin decreases mortality in **Lassa fever** and in **hemorrhagic fever** with renal syndrome. The intravenous use of ribavirin is investigational.

Adverse effects

- Ribavirin is contraindicated for patients requiring mechanical ventilation because the small aerosol particles precipitate on the respirator valves and tubing, causing malfunction that can be lethal.
- Rash and conjunctivitis have occurred with aerosol use.
- Ribavirin is mutagenic, teratogenic, and possibly carcinogenic.

Human Interferon's: They are the cytokines produced by host cells in response to viral infections. There are three types α , β and γ interferon's in man. They also have immunomodulating and antiproliferative properties. They inhibit the multiplication of many DNA and RNA viruses.

Chemistry

- Interferons are naturally occurring glycoproteins that can be produced by almost any mammalian cell type, including lymphocytes and fibroblasts, when the cells are stimulated in the inflammatory process.
- Interferons are of three major classes; those used clinically are alpha α -interferons.

Mechanism of action

- The antiviral, antitumor effects of interferons are thought to result from the induction of enzymes that inhibit the synthesis of proteins and DNA.
 - Interferon-treated cells develop the ability to block viral replication.

- Interferon is able to suppress cell proliferation.
- Interferon also has immunomodulating effects.
 - i. It enhances phagocytosis by macrophages.
 - ii. It increases the target-cell-specific cytotoxicity exerted by lymphocytes.
- The antiviral effect takes several hours to develop after interferon treatment.

Therapeutic uses

- Interferon preparations are currently used for the treatment of:
 - Hairy-cell leukemia
 - AIDS-related Kaposi's sarcoma in AIDS Patients
 - Genital (venereal) warts (condylomata acuminata) by Papilloma virus
- In patients with lymphoma, early treatment of a herpes zoster infection with interferon appears to prevent the spread of infection.
- Treatment with interferon can induce clinical remission in 30%-40% of patients with chronic hepatitis B. Interferon can also cause improvement in patients with hepatitis C or D virus; however, relapse occurs in patients with chronic hepatitis D when treatment is stopped.
- Interferon-alpha (IFN- α) has been applied topically in herpes kerato-conjunctivitis in combination with acyclovir and trifluridine.
- Rhinovirus (cold) interferon α is given intranasal for prophylaxis.

Preparations and administration

- Two recombinant products are available: interferon alpha-2a and interferon alpha-2b; they differ by only one amino acid residue.
- Administration is by the intramuscular or subcutaneous route, or intralesionally into genital warts.

Adverse effects

- The plasma concentration of hepatic enzymes increases.
- Influenza-like symptoms (i.e., fever, chills, myalgias) occur minutes to hours after parenteral administration; they are self-limited.
- Progressive fatigue is the most common dose-limiting adverse effect when administered chronically.
- Interferon in high doses acts as an abortifacient in primates.
- The metabolism of other drugs can be reduced by interferon's action on the cytochrome P-450 system.
- Bone marrow suppression with granulocytopenia and thrombocytopenia is common.

Vidarabine (adenine arabinoside): Though approved for the treatment of herpes simplex virus and varicella-zoster virus, vidarabine has been largely replaced by acyclovir.

Vidarabine may be carcinogenic and should not be used to treat minor infections.

Bird Flu

Alternative names Bird Flu: H5N1

Definition

Avian influenza is flu infection in birds. The disease is of concern to humans, who have no immunity against it. The virus that causes this infection in birds can mutate (change) to easily infect humans. Such mutation can start a deadly worldwide epidemic.

Causes, incidence, and risk factors

Historically, avian influenza viruses infected pigs and mixed with pig influenza viruses. The viruses exchanged genetic information, which led to the formation of a new virus. This new virus could then infect humans and easily spread from person-to-person. Previous flu pandemics (worldwide epidemics) have started this way.

The first avian influenza virus to infect humans directly occurred in Hong Kong in 1997, during an avian flu epidemic on the island. This outbreak was linked to chickens and classified as avian influenza A (H5N1).

Farmers and other people working with poultry, as well as travellers visiting affected countries, have a higher risk for getting the bird flu. Handling an infected bird can cause infection. People who eat raw or undercooked poultry meat are also at an increased risk for avian influenza. Highly infective avian flu viruses, such as H5N1, increased risk for avian influenza. Highly infective avian flu viruses, such as H5N1, have been shown to survive in the environment for long periods of time, and infection may be spread simply by touching contaminated surfaces. Birds who recover from the flu can continue to shed the virus in their feces and saliva for as long as 10 days.

Health care workers and household contacts of patients with avian influenza may also be at an increased risk of the bird flu.

Symptoms (Fig. 12.12.2)

Symptoms of avian flu infection in humans depends on the particular strain of virus. In case of the H5N1 virus, infection in humans causes more classic flu-like symptoms, which might include:

- Cough (dry or productive)
- Sore throat
- Fever > 100.4°F (38°C)
- Difficulty in breathing

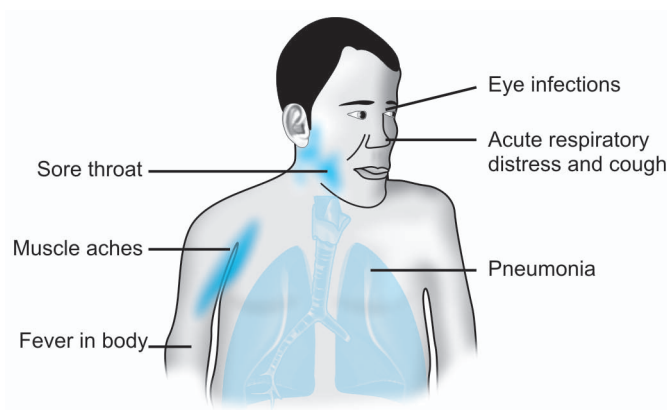


Fig. 12.12.2: Clinical features of avian influenza

- Diarrhea
- Runny nose
- Headache
- Malaise
- Muscle aches

Tests

Doctor might perform the following tests:

- Chest X-ray
- Nasopharyngeal culture
- Blood differential count
- Auscultation (to detect abnormal breath sounds)

Depending on symptoms and their severity, other tests may be performed to assess the functions of heart, kidneys and liver.

Treatment

Treatment with the antiviral medication oseltamivir (**Tamiflu**), and perhaps zanamivir (**Relenza**), may be started within 48 hours after symptoms begin. **Oseltamivir** may also be prescribed for household contacts of people diagnosed with avian flu. Samples of H5N1 from human infections proved resistant to the antiviral medications **amantadine and rimantadine**. Therefore, these medications cannot be used if and H5N1 outbreak occurs.

People with severe infection may need breathing assistance with mechanical ventilation. It is currently recommended that people diagnosed with H5N1 infection be put in isolation.

Because different types of avian flu virus may cause different symptoms, treatment may vary.

Currently, there is no available vaccine against avian influenza. However, a vaccine against H5N1 is being tested in clinical trials.

Swine Flu

Novel H1N1 (referred to as “**swine flu**” early on) is a new influenza virus causing illness in people. This new virus was first detected in people in the United States in April 2009. Other countries, including Mexico and Canada, have reported people sick with this new virus. This virus is spreading from person-to-person, probably in much the same way that regular seasonal influenza viruses spread.

This virus was originally referred to as “**swine flu**” because laboratory testing showed that many of the genes in this new virus were very similar to influenza viruses that normally occur in pigs in North America. But further study has shown that this new virus is very different from what normally circulates in North American pigs. It has two genes from flu viruses that normally circulate in pigs in Europe and Asia and avian genes and human genes. Scientists call this a “**quadruple reassortant**” virus.

CDC has determined that novel H1N1 virus is contagious and is spreading from human-to-human. However, at this time, it is not known how easily the virus spreads between people.

Clinical Manifestations

The symptoms of novel H1N1 flu virus in people are similar to the symptoms of **seasonal flu and include fever, cough, sore throat, runny or stuffy nose, body aches, headache, chills and fatigue**. A significant number of people who have been infected with this virus also have reported diarrhea and vomiting. Also, like seasonal flu, severe illnesses and death has occurred as a result of illness associated with this virus.

Warning Signs

In children, emergency warning signs that need urgent medical attention include:

- Fast breathing or trouble breathing
- Bluish or gray skin color
- Not drinking enough fluids
- Severe or persistent vomiting
- Not waking up or not interacting
- Being so irritable that the child does not want to be held
- Flu-like symptoms improve but then return with fever and worse cough

In adults, emergency warning signs that need urgent medical attention include:

- Difficulty breathing or shortness of breath
- Pain or pressure in the chest or abdomen

- Sudden dizziness
- Confusion
- Severe or persistent vomiting
- Flu-like symptoms improve but then return with fever and worse cough

Treatment

CDC recommends the use of **oseltamivir** or **zanamivir** for the treatment and/or prevention of infection with novel H1N1 flu virus. Antiviral drugs are prescription medicines (pills, liquid or an inhaled powder) that fight against the flu by keeping flu viruses from reproducing in your body. If you get sick, antiviral drugs can make your illness milder and make you feel better faster. They may also prevent serious flu complications. During the current outbreak, the priority use for influenza antiviral drugs during is to treat severe influenza illness.

1. **Oseltamivir (brand name Tamiflu®)** is approved to both treat and prevent influenza A and B virus infection in people one year of age and older.
2. **Zanamivir (brand name Relenza®)** is approved to treat influenza A and B virus infection in people 7 years and older and to prevent influenza A and B virus infection in people 5 years and older.

Prevention

Influenza antiviral drugs also can be used to prevent influenza when they are given to a person who is not ill, but who has been or may be near a person with swine influenza. When used to prevent the flu, antiviral drugs are about 70% to 90% effective. When used for prevention, the number of days that they should be used will vary depending on a person's particular situation.

Antifungal Drugs

Fungal infections may be classified as:

- a. Systemic or
- b. Superficial (topical).

Classification of Fungal Infection

Deep mycosis

- *Coccidioidomycosis*
- *Aspergillosis*
- *Blastomycosis*
- *Sporotrichosis*
- *Histoplasmosis*
- *Cryptococcosis*

Superficial Mycosis

- **Candidiasis**
 - Cutaneous candidiasis
 - Vulvovaginal candidiasis
 - Oropharyngeal candidiasis
- **Ring worm**
 - Topical infection
 - Systemic infection

In the recent years, there has been an increase incidences of fungal infections. Due to the Iatrogenic infections, i.e. use of broad spectrum antibiotics and anticancer drugs, various unusual and drug-resistant organisms have emerged, therefore their treatment is essential.

HISTORY

- 1950: Increase in the incidences of iatrogenic fungal infection leads to development or introduction of :
 1. *Amphotericin-B* (1956): Specially for the treatment of systemic mycosis.
 2. *Griseofulvin* (1960's): For the treatment of Dermatophytes
- 1970: [Early] – Flucytosin
- 1970: [mid] – Imidazoles

- 1980: – Triazoles were introduced
- 2000: – Caspofungin
- Latest: – Terbinafine

CLASSIFICATION

1. Antibiotics

Polyenes: Amphotericin B, Nystatin, Hamycin, Natamycin

Benzofuran: Griseofulvin.

2. Antimetabolites: Flucytosine (5-FC)

3. Azoles

Imidazoles: [Topical] Clotrimazole, Miconazole, [Systemic] Ketoconazole

Triazoles: [Systemic] Fluconazole, Itraconazole

4. Allylamine: Terbinafine, (latest) Nifitine

5. Other topical agents: Tolnaftate, Benzoic acid, Undecylenic acid, Selenium sulfide, etc.

Antifungal Antibiotics

Amphotericin B: It is obtained from *Streptomyces nodosus* in 1956 by **Gold and Coworkers**.

Chemistry: It is a Amphoteric (amphi-philic) polyene macrolid antibiotic, containing many double bonds and large lactone ring of >12 C atoms. .

Spectrum of activity

- Antifungal spectrum: “Amphotericin B” has a wide antifungal spectrum. It inhibits the growth of *Histoplasma capsulatum*, *Aspergillus*, *Candida albicans*, *Cryptococcus neoformans*, *Coccidioides*, and *Blastomyces dermatitidis*.
- It is also active against (responsible for kala-azar) *Leishmania*

Mechanism of action

- ***It is fungistatic at low and fungicidal at high concentrations.***

Amphotericin B binds to ergosterol, which is present in high concentration in fungal and yeast cell membranes and forms micro pores in them (cell membrane). Through these pores, cell contents like electrolytes, ions, water, etc. leak out resulting in cell death.

Pharmacokinetics

- Amphotericin B is not absorbed orally. It can be given orally for treating intestinal candidiasis without systemic toxicity.
- > 90% bound to plasma protein
- If given IV, it has wide distribution in the body and has a long $t_{1/2}$ of 15 days.
- 60% of the drug is slowly excreted in the urine.

Therapeutic uses

- Amphotericin B is available for systemic fungal infections.
- It is frequently used for the treatment of life-threatening fungal infections in patients with impaired defense mechanisms (e.g., patients undergoing immunosuppressive therapy or cancer chemotherapy, and patients with AIDS). Flucytosine is sometimes given with amphotericin B for the initial treatment of rapidly progressive, life-threatening fungal infections.
- Amphotericin B is used in the treatment of the following infections:
 - Pulmonary, cutaneous, and disseminated forms of blastomycosis.
 - Acute pulmonary coccidioidomycosis.
 - Pulmonary histoplasmosis.
 - *C. neoformans* infections: the most common life-threatening fungal pathogen associated with AIDS
 - Candidiasis, including disseminated forms
- In addition, mucocutaneous lesions of parasitic American leishmaniasis may respond to amphotericin B therapy.
- Intrathecal infusion may be useful in the treatment of fungal meningitis in a dose of 0.5 mg twice weekly for 10 weeks.
- To treat corneal fungal ulcers (1 mg/ml solution will be instilled in eyes and repeated in the 30 to 60 minutes).

Preparations

- Lyophilized powder for injection is available
- Topical formulations are also available like:
 - ABLC : Amphotericin B lipid complex
 - ABCD : Amphotericin B colloidal dispersion
 - LAB : Liposomal Amphotericin B

Adverse effects

- ***Hypersensitivity reactions*** (anaphylaxis)
- Fever, chills, muscle spasms, vomiting, **headache** hypotension, and gastrointestinal disturbances are common with IV infusion.
- Renal impairment (**Nephrotoxicity**) **i.e. decreased renal function** and **anemia due to bone marrow depression** can also occur.
- Normochromic normocytic **anemia** and
- Thrombophlebitis can occur.

Nystatin: It is obtained from *Streptomyces noursei*

Chemistry: Nystatin is a polyene antibiotic.

Mechanism of action

- The drug is fungistatic at lower concentration and fungicidal at higher concentration.
- It binds to sterols, especially ergosterol, which is enriched in the membrane of fungi and yeasts. As a result of this binding, the drug appears to form channels in the membrane that allow small molecules to leak out of the cell.

Pharmacokinetics

- It is not employed parenterally.
- It is not absorbed from the skin or mucous membranes.
- Nystatin is not absorbed appreciably from the gastrointestinal tract.

Therapeutic uses

- Nystatin is used to treat Candidal infections of the skin, mucous membranes, and intestinal tract.
- Thrush (oral candidiasis) and vaginitis are treated by topical application, whereas intestinal candidiasis is treated by oral administration.
- **Preparations.** Nystatin is supplied as an ointment, oral suspension, oral tablets, drops, and powder.

Adverse effects: Occasional gastrointestinal disturbances occur with oral administration.

Hamycin

- It is also similar to nystatin.
- It has higher water solubility
- It is used topically for cutaneous candidiasis and otomycosis.

Griseofulvin: Griseofulvin is the antifungal given orally for superficial dermatophytes.

Chemistry: It is a fungistatic derived from *Penicillium griseofulvum* in 1939.

It is effective in superficial dermatophytosis caused by:

- *Trichophyton*,
 - *Microsporum* and
 - *Epidermophyton*
- } *Tinea*

Pharmacokinetics

- Griseofulvin is absorbed in the upper part of the small intestine following oral administration. Most of the drug is eliminated after methylation (metabolism) in the urine.
- Griseofulvin has a particular affinity for keratin. It gets deposited in the newly forming skin, binds to keratin and protects the skin from getting newly infected.

Mechanism of action

- It interfere with mitosis and it also causes abnormal metaphase configuration, i.e. it does not arrest metaphase, but it inhibit movement of daughter cells apart.
- It is fungistatic not fungicidal

Adverse effects

- Toxicity is very less and not of serious type.
- They includes allergic reactions, hepatitis and neurotoxicity.
- Headache, photo allergy, and leucopenia are the important adverse side effects.

Uses: Griseofulvin is used in superficial dermatophytosis. Because of its affinity for keratin, griseofulvin is useful for treating mycotic diseases of the skin, hair, and nails, such as tinea capitis, pedis (athlete's foot), cruris, corporis, and circinata. It is given orally; topical use has little effect.

Antimetabolites

Flucytosine (5 FC): It is a fluorinated pyrimidine, effective against *cryptococcus neoformans* and some strains of *Candida*.

Chemistry: This drug is a fluorinated pyrimidine.

Mechanism of action: Flucytosine is converted within fungal cells (but not in the host's cells) to **5-fluorouracil**, which again converted into **5 fluorodeoxyuridylic acid** a metabolic antagonist that ultimately leads to inhibition of *thymidylate synthetase (enzyme)*, which ultimately *inhibits DNA synthesis (fungal)*.

Pharmacokinetics

- Flucytosine is well absorbed from the gastrointestinal tract and is distributed widely throughout the body, including the cerebrospinal fluid (CSF)
- It is excreted in the urine, mainly in unchanged form

Pharmacological effects

- The drug is effective against *cryptococcus neoformans*.

- It is effective against some strains of *Candida albicans*. However, *C. albicans* can become resistant to flucytosine during therapy.

Therapeutic uses

- Flucytosine is not as effective as amphotericin B and is generally not used alone. It is used with Amphotericin B (if used alone, resistance develops rapidly) in cryptococcal meningitis and systemic candidiasis.
- It is used for systemic infections caused by *C. albicans* and *C. neoformans* (*Cryptococcus meningitidis*), most often in combination with amphotericin B.

Preparations: Flucytosine is available as capsules for oral use.

Adverse effects have included:

- Fatal bone marrow depression (Uretil is reported to reduce this effect).
- Gastrointestinal distress, especially when given with amphotericin B
- Skin rashes and alopecia.
- Hepatic dysfunction (hepatitis)
- Anemia, neutropenia and thrombocytopenia.

Azoles

Imidazoles and Triazoles: The older antifungal agents need to be given intravenously and are quite toxic. Azoles are newer antifungals that are effective orally and are less toxic.

- Antifungal spectrum: Azoles have a broad spectrum of antifungal activity.
- They inhibit dermatophytes, candida, cryptococcus neoformans and other deep mycoses.

Mechanism of action: Azoles inhibit fungal cyt. P450 enzyme; *lanosterol-14-demethylase* and ultimately inhibit (impairs) the synthesis of ergosterol, an important component of the fungal cell membrane.

Of the azoles, clotrimazole and miconazole are used only topically.

1. Clotrimazole

- Used topically in the treatment of Athletes foot, Otomycosis, oral, cutaneous and vaginal candidiasis.
- It has no specific toxicity.
- Clotrimazole troche is available for oral thrush.
- Clotrimazole (CANDID, CLODERM) Lotion, cream, vaginal pessary are also available

2. Econazole

- Same as above with additional higher penetration to superficial layers.
- No specific adverse effect except mild irritation.

3. Miconazole

- Highly effective (more efficacy).
- More deep penetration. (comparatively)
- Cure rate is > 90%.
- **Uses:** Tinea, pytriasis, otomycosis, cutaneous and vaginal candidiasis.
- **Side effects:** Mild irritation and pelvic cramps are the important one.
- **Preparation:** Miconazole (DAKTARIN ZOLE).

Ketoconazole (KTZ)

- It is the first oral azoles to be available.
- It is well-absorbed from the gut. Food and low gastric pH enhance absorption.
- In large doses it inhibits the biosynthesis of adrenal and gonadal steroids in humans resulting in gynecomastia, infertility and menstrual irregularities.

Adverse reactions: Include gastric irritation, headache, allergic reactions, gynecomastia, infertility, menstrual irregularities and rarely hepatotoxicity. It is C/I in Pregnancy.

Preparations: FUNGICIDE, NIZRAL—ointment, shampoo, and 20 mg tablets are available.

Drug interactions

- Rifampicin and phenytoin induce KTZ metabolism and decrease its efficacy.
- **Ketoconazole increases arrhythmogenic effects of terfenadine and astemizole** by increasing their blood levels.

Uses: Mucocutaneous candidiasis and dermatophytosis can be treated with ketoconazole. It is also useful in Cushing's syndrome.

Fluconazole

- It is water soluble agent,
- Well-absorbed orally and attains good CSF concentration.
- It has wider range of activity than KTZ.

Adverse effects

- They are mild gastrointestinal disturbances, headache and rashes.
- Since it has very little effect on hepatic microsomal enzymes, drug interactions are less common but it may produce serious **Ventricular tachycardia with Cisapride**.
- It is contraindicated in pregnancy.

Uses

- Fluconazole is used in cryptococcal meningitis, systemic candidiasis and other systemic fungal infections.

- Though it is also effective in tinea infections and mucocutaneous candidiasis, its higher cost makes it less preferable.

Itraconazole

- It is the most potent azoles.
- It is a broad spectrum antifungal agent
- If given orally, its absorption is increased by food and gastric acid.
- Its effect on hepatic microsomal enzymes is less; does not affect steroid synthesis. Thus it is preferred over ketoconazole.
- It is useful in dermatophytosis, candidiasis, aspergillosis and onychomycosis
- (ITASPOR, SPORANOX 100 mg cap).

Terbinafine

- It is a new synthetic (allylamine class) of antifungal drug that is effective against dermatophytes and Candida.
- It is orally effective and is fungicidal.
- Its absorption is about 75%.
- It is lipophilic and has wide distribution.
- Metabolized in liver and excreted 80% in urine while 20% in faeces.
- It gets concentrated in the keratin like griseofulvin.

Mechanism of action: It inhibits an enzyme needed for biosynthesis of ergosterol by fungi.

Adverse effects: They are rare; gastrointestinal disturbances, rashes and headache are some important adverse effects.

Uses: Terbinafine is used in dermatophytosis, pityriasis, onychomycosis and candidiasis. SEBIFIN—250 mg tab, 1% cream.

Other Topical Antifungal Agents: Apart from Nystatin, Clotrimazole, Miconazole and Terbinafine, some drugs like:

Salicylic acid, Benzoic acid, Tolnaftate, Cyclopirox olamine are used topically for dermatophytosis and pityriasis versicolor.

Mechanism of action: Usually these topical antifungal agents act by their hyperkeratolytic action, irritation and counterirritation.

Selenium sulfide: Is useful in tinea versicolor caused by *Malassezia furfur*, and also in dandruff. SELSUN is 2.5% suspension of selenium sulfide in a shampoo base. It is irritant to the eyes and the odor is unpleasant. Sodium thiosulfate is also used for the same purpose.

Whitefields ointment: It is a combination of Benzoic acid 5% + Salicylic acid 3%. It has keratolytic action.

Antiamoebic Drugs

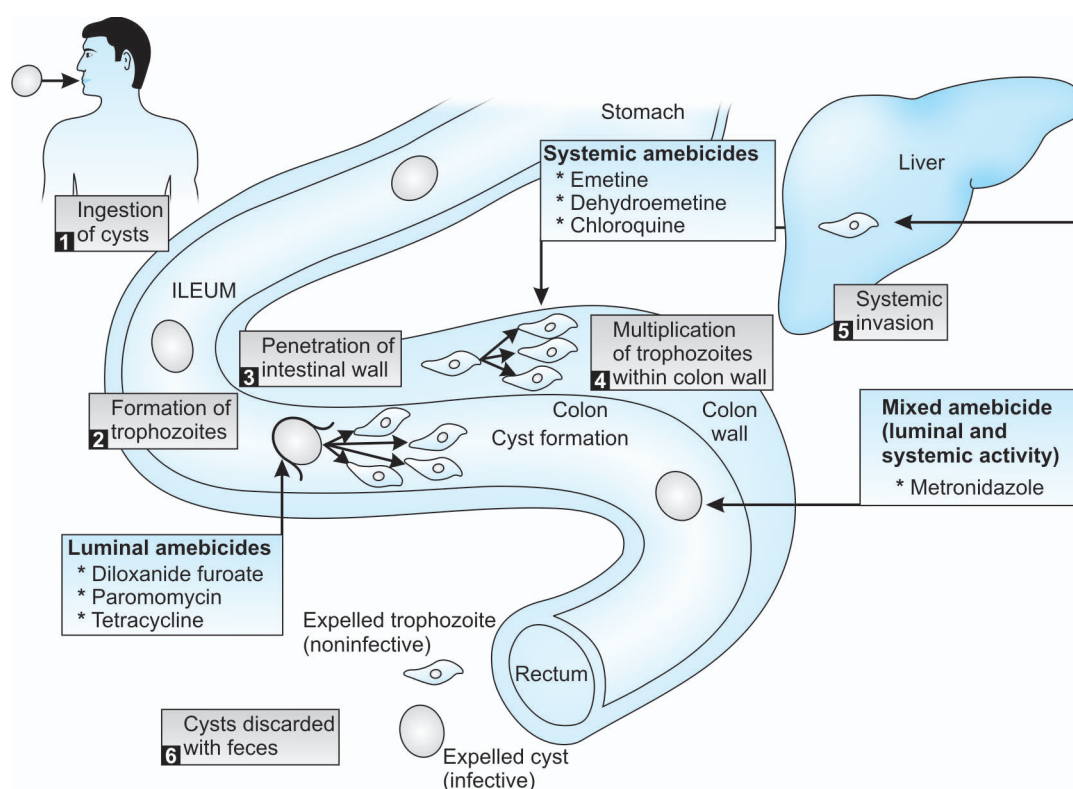


Fig. 12.14.1: Life cycle of *Entamoeba histolytica* showing sites of action of amoebicidal drugs

ANTIAMEBIC DRUGS

Amebiasis (Fig. 12.14.1)

It is an infectious protozoan disease. Both intestinal and extraintestinal form of amebiasis are caused by *Entamoeba histolytica*. It is common in (tropical region) developing countries. It is a primary disease of large intestine (colon), other organs like liver, lungs and brain are also secondarily involved once the disease advances. It spreads by faecal contamination of food and water.

The disease is classified into:

Acute amebiasis: It is characterized by bloody mucoid stools and colicky pain in abdomen and a persistent desire to pass stool.

Chronic amebiasis: It manifests as anorexia, mild abdominal pain or heaviness, intermittent diarrhea and constipation. Cyst passers or carriers are usually symptom free or are having very mild unnoticeable manifestations.

CLASSIFICATION OF DRUGS

1. Drugs used in intestinal amebiasis

Nitroimidazoles

- Metronidazole
- Tinidazole
- Ornidazole
- Secnidazole

Halogenated hydroxyquinolines

- Diiodohydroxyquinoline
- Iodochlorohydroxyquinoline
- Hydroxyquinoline

Emetine

Dehydroemetine

Diloxanide furoate

Antibiotics

- Paromomycin
- Etracyclines
- Erythromycin

2. Drugs used in extraintestinal amebiasis

- Nitroimidazoles
- Chloroquine
- Emetine

Metronidazole

- It is a nitroimidazole, is a powerful amebicide.
- Apart from this it also inhibits *Trichomonas vaginalis*, *Giardia lamblia* and *Balantidium coli*. Anaerobic bacteria are also sensitive.

Mechanism of action

- It is readily taken up by sensitive protozoa and anaerobic bacteria. In these organisms, its nitro group is chemically reduced by ferridoxin into products which are lethal to these organisms by reacting with various macromolecules interacts with free radicals; it has a radio-sensitizing effect on tumor cells.

Pharmacokinetics

- On oral administration, it is rapidly absorbed and reaches adequate concentrations in the CSF.
- Protein binding is 20% and it is metabolized in the liver.
- Plasma half-life is 7.5 hours. It is excreted in urine.

Adverse effects

- Nausea, anorexia, abdominal pain and metallic taste in the mouth are most common.
- Headache, stomatitis, dizziness, insomnia, skin rashes and rarely peripheral neuropathy can occur.
- Higher doses can cause convulsions.
- Thrombophlebitis at the site of injection.

Metronidazole has a disulfiram like effect; on alcohol intake, antabuse like reaction can follow.

Uses

- 1. Amebiasis:** It is effective and drug of choice in all forms of amebiasis. It is given in doses of 400-800 mg three times a day for 5-7 days. In children, the doses are 35-50 mg/kg per day in divided doses. But it does not eradicate the cysts.
- 2. Giardiasis:** Metronidazole given 400 mg TDS for 7 days is the drug of choice.
- 3. Trichomonas vaginitis:** Metronidazole 400 mg TDS for 7 days is the drug of choice.
- 4. H. pylori infections in peptic ulcer:** Patients can be treated with a combination of metronidazole, clarithromycin and omeprazole/ranitidine (triple drug regimen)
- 5. Pseudomembranous colitis:** due to *Clostridium difficile*
- 6. Acute ulcerative gingivitis:** As an alternative to penicillin G.
- 7. Dracunculosis:** Metronidazole facilitates extraction of the guinea worm.
- 8. Anaerobic infections:** Metronidazole is given intravenously for serious anaerobic infections. It is also useful for surgical prophylaxis. The recommended dose is 15 mg/kg initially IV which is followed by 6 hours later with a maintenance dose of 7.5 mg/kg IV every 6 hours for 7-10 days. For other infections, it is used in doses of 250 mg orally three times a day for 5-7 days. **Pericoronar abscess and periodontal abscess are treated with a combination of metronidazole with ciprofloxacin/amoxicillin.**

Tinidazole

- It is structurally related to metronidazole and have similar therapeutic range
- It is longer-acting and is better tolerated than metronidazole due to lesser side effects and less frequent administration.
- It can be given 2 gm once daily for 3 days in amebiasis and as a single dose for other indications.

Secnidazole and Ornidazole

- They are also structurally related to metronidazole and has similar therapeutic range.
- It is longer-acting and can be given as a single 2 gm dose for most indications of metronidazole.
- Adverse effects are less, but metallic taste and headache are important side effects. Although it is more

convenient, other drugs with lesser half life are much safer to use specially in renal patients.

- Ornidazole is given in a dose of 500 mg twice daily for 5-10 days.

Diloxanide Furoate

It is directly acting amebicidal agent.

- As diloxanide eradicates cysts, it is used alone in asymptomatic cyst passers, mild intestinal amebiasis and along with a nitroimidazole: for the cure of amebiasis.
- On oral administration, it is rapidly absorbed, undergoes glucuronide conjugation and excreted in urine.
- Nausea, flatulence, occasionally abdominal cramps, vomiting, dryness of mouth, urticaria, diarrhea and tingling sensations may occur as side effects.
- It is given orally—500 mg TDS for 10 days.
- It is also available in combination with metronidazole (DYRADE-M).
- It is not recommended during pregnancy and children below 2 years of age.

Emetine and Dehydroemetine

Since emetine has a narrow margin of safety and produces severe cardiovascular and gastrointestinal side effects, its use has large been replaced by metronidazole.

- They are derived from ipecac (Brazil root)
- Oral absorption is improper, therefore they are given parenterally. They can be used only in severe amebiasis. It directly affects the trophozoites but not the cysts.
- **Adverse effects** include nausea, vomiting, diarrhea and cardiotoxicity. Pain and thrombophlebitis at the injection site.
- Emetine hydrochloride is given by deep subcutaneous or intramuscular injection in doses of 30-60 mg daily for 10 days to treat acute amebic dysentery.
- Emetine bismuth iodide is given orally in a dose of 60-120 mg daily for 12 days.
- **Dehydroemetine:** It is equally effective but less toxic due to its more rapid excretion and lower concentration in cardiac tissue. It is given in a dose of 1.0 mg/kg IM daily for 5-10 days.

Chloroquine

- Since it attains high concentration in the liver and lung, it is directly toxic against trophozoites and is therefore useful in hepatic and pleuropulmonary amebiasis.
- As chloroquine is completely absorbed from the small intestines, it is not effective against amoebae in the colon.

- The recommended dose is 1 gm daily for 2 days followed by 500 mg daily for 2-3 weeks.
- A luminal amebicide should also be given. Better results are seen in combination with emetine and metronidazole.

Halogenated Hydroxyquinolines

Iodoquinol and quiniodochlor (8-hydroxyquinolines):

This group includes diiodohydroxyquinoline (iodoquinol), iodochlorohydroxyquinoline (vioform), hydroxyquinoline, and chlorohydroxyquinoline.

- They are directly acting luminal amebicides.
- They are used as alternative drugs for the treatment of asymptomatic or mild to moderate amebiasis. They were used for eradication of cysts but are not preferred now due to their toxicity.
- They are also effective against giardiasis and *E. coli* infection.
- Their absorption in the gut is variable and most of the drug is excreted in the feces.
- The dose of halogenated quinolines varies from 600-750 mg daily in divided doses for 10-20 days.
- Commonest side effects are nausea, vomiting, skin rash, fever and peripheral neuropathy. Optic neuritis, optic atrophy and subacute myelo-optic neuropathy (SMON) have been reported with iodoquinol in Japan after long-term use.

ANTIBIOTICS

Tetracyclines and Erythromycines

Tetracyclines and erythromycin act indirectly by inhibiting the normal flora. They are used as adjunct to main drugs.

- The older tetracyclines are not well-absorbed and large amounts reach the colon; these are useful in intestinal amebiasis.
- They inhibit the intestinal flora and break the symbiosis between them and the amoebae.
- Tetracyclines should not be used during pregnancy and in children under 8 years of age.

Paromomycin is an aminoglycoside.

- It has direct amebicidal property as well as acts indirectly by inhibition of normal intestinal flora essential for the multiplication of the amoeba.
- It is not absorbed from gut. It is given in doses of 25-35 mg/kg in divided doses at meal for 7 days. It may cause diarrhea, renal damage and ototoxicity.

Treatment of different forms of amebiasis

1. Acute intestinal amebiasis—one of the following can be given.

- Metronidazole 400-800 mg TDS for 5-7 days (METROGYL)
- or
- Metronidazole 2.4 gm OD for 3 days
- or
- Tinidazole 2 gm OD for 3 days (TINIBA)
- or
- Secnidazole 2 gm single dose (SECZOL).

This should be followed by diloxanide furoate 500 mg TDS for 10 days to eradicate the cysts.

2. Chronic amebiasis

Diloxanide furoate 500 mg TDS for 10 days or tetracycline 250 mg qid for 10 days.

3. Hepatic amebiasis

This condition requires intensive treatment for the complete eradication of the *Entamoeba histolytica* from the liver in order to avoid relapse.

A course of **metronidazole** or tinidazole are the first line drugs.

Additionally **Chloroquine** may be given to ensure complete destruction of the liver forms.

A course of diloxanide furoate should follow in order to eradicate the cysts.

Giardiasis

Flagellate protozoan *G. lamblia* is responsible for causing giardiasis. Mostly it lives as a commensal in the intestine. However, sometimes it causes diarrhea and requires treatment. Effective drugs are:

- **Metronidazole**: It is drug of first choice. Dose: 400 mg three times a day for seven days.

- **Tinidazole**: Dose: 2 gm as single dose.
- **Secnidazole**: Dose: 2 gm as single dose.
- **Furazolidone (Furoxone)**: It is a 5-nitrofur derivative. It is highly effective against gram-negative bacteria including *Salmonella* and *Shigella* and some protozoa such as *Giardia* and *Trichomonas*.
- It is partly absorbed on oral administration and partly excreted in urine. It imparts orange color to the urine. It is given in a dose of 100 mg four times a day for 5-7 days to treat bacterial enteritis, giardiasis, food poisoning, bacillary dysentery and diarrhea. It is employed as an alternative drug to treat typhoid fever in a dose of 200 mg 4 times a day for 2 weeks. It is used in combination with infuroxine for topical treatment (as a powder or suppository) of vaginal trichomoniasis and candidiasis. It causes nausea, vomiting, diarrhea, skin rash and disulfiram-like effect as side effects.

Being toxic, mepacrine is no more used in giardiasis and malaria.

Trichomoniasis

Vulvovaginitis is caused by *Trichomonas vaginalis*.

Effective drugs are:

- **Metronidazole** (drug of choice): Dose: 400 mg twice daily for 7 days.
- **Tinidazole**: Dose: 0.3 gm once daily for 7 days or 2 gm as a single dose.
- Intravaginal drugs are metronidazole, hamycin, clotrimazole and iodoquinol.
- **Nifurtimox**: It is a nitrofur derivative which is used to treat acute as well chronic forms of American trypanosomiasis. On oral administration, it is readily absorbed from gut and is rapidly metabolized.

Chemotherapy of Malaria

Malaria is caused by protozoa of the genus *Plasmodium*, transmitted through the bite of a female *Anopheles* mosquito. It is a major public health problem in most of the developing countries including India.

- Four species of protozoa *Plasmodium* (*P. vivax*, *P. falciparum*, *P. malariae* and *P. ovale*) cause malaria.
- Two commonest forms of malaria are **benign tertian** (BT) and **malignant tertian** (MT). The former is caused by *P. vivax* and the later by *P. falciparum*. In both the types, the infected individual develops fever, with rigors every third day and are called “Tertian”.
- Infections due to *P. ovale* and *P. malariae* are not common in man.
- A large number of sporozoites are present in the salivary glands of the infected female anopheles mosquitoes. An individual is infected by malarial parasites through the bite of a female anopheles mosquito. Sporozoites thus inoculated into the blood stream disappear rapidly from the circulation and invade the parenchymatous cells of the liver and the reticuloendothelial cells.
- They multiply there to form tissue schizonts (primary exoerythrocytic form or pre-erythrocytic stage). After this stage (incubation period 5-7 days in *P. falciparum* and 8 days to several months in *P. vivax*), merozoites are released into the blood stream. They can invade erythrocytes and undergo further developments and multiplication giving rise to erythrocytic schizonts (a sexual erythrocytic stage) known as trophozoites.
- Eventually infected blood cells rupture and release merozoites along with metabolic and toxic substances which cause fever with chills and rigor followed by feeling of heat and sweating. The merozoites released in blood may invade fresh erythrocytes to undergo erythrocytic schizogony repeatedly; some of them are differentiated into male (microgametocyte) and female (macrogametocyte) sexual forms which when taken by another female mosquito develops into zygotes to form oocyst

which ultimately gives rise to sporozoites. In case of *P. vivax* infection, some of them enter new liver cells and continue exoerythrocytic stage. They are termed as hypnozoites which are responsible for relapses. (Fig. 12.15.1)

Classification of Antimalarial Drugs according to their Chemical Structure

4-Amoniquinoline

- Chloroquine
- Amodiaquine
- Hydroxychloroquine

8-Aminoquinoline

- Primaquine
- Bulaquine

Diaminopyrimidine

- Pyrimethamine
- Trimethoprim

Biguanide (folate antagonists)

- Proguanil
- Chlorproguanil
- Cycloguanil

4-Quinoline Methanol

- Mefloquine
- Halofantrine, Lumefantrine (amino alcohol)

Cinchona Alkaloids

- Quinine, Quinidine.

Sulfonamide and Sulphone

- Sulfadoxine
- Sulfalene
- Sulfamethoxazole
- Dapsone

Acridine

- Mepacrine

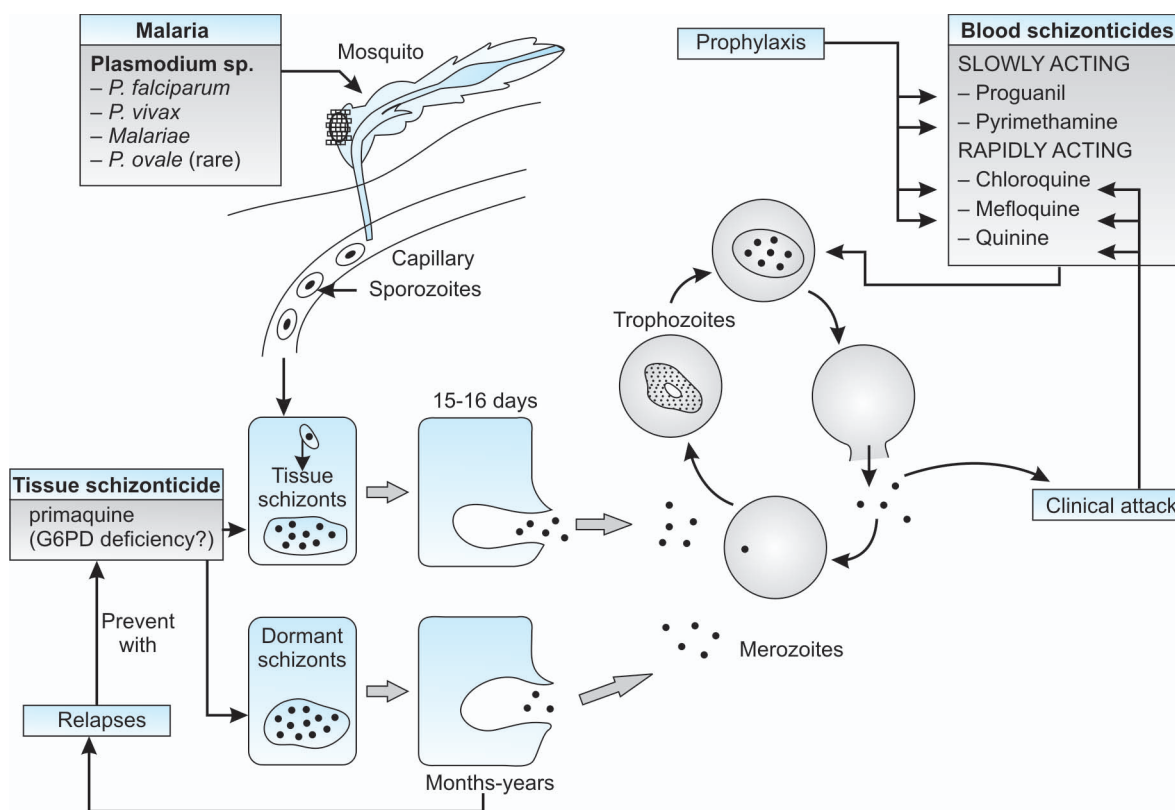


Fig. 12.15.1: Life cycle of malaria parasite

Miscellaneous

- Artemisinin
- Yinghaosu
- Doxycycline

Tetracyclines (doxycyclines)**Artemisinin****Norfloxacin**

Eradication of malaria may be done by the use of drugs in the following ways (Fig. 12.15.1):

- 1. Causal Prophylactics: Primaquine, Pyrimethamine**
 These destroy the tissue forms of the parasite in liver cells and prevent invasion of the erythrocytes. They are also called primary tissue schizonticides. There is no drug (true causal prophylactic) available, which can kill the sporozoites before they can infect the cells of reticuloendothelial system.
- 2. Blood schizontocides (suppressives): Chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, chloroguanide and artemisinin.**

Suppressives act at erythrocytic stage, destroy erythrocytic forms and terminate clinical attacks of malaria.

3. Tissue schizontocides used to prevent relapse: primaquine

They act on hepatic forms of *P. vivax* and *P. ovale* that produce relapses. Given with a blood schizonticide, they bring about radical cure and eradicate the parasite from the body in these relapsing malarial infections.

4. Gametocidal drugs: Primaquine, chloroquine and quinine.

They destroy the sexual forms of malarial parasites and eradicate both the vivax and falciparum gametocytes. These prevent the transmission of malaria.

Clinical cure – It is achieved by schizontocides which interrupt erythrocytic and exoerythrocytic schizogony of the malarial parasite and terminates the clinical attack.

Radical cure – It is achieved by drugs which act at both erythrocytic and exoerythrocytic parasites. Primaquine may be used with chloroquine for better results. Prolonged use of

suppressive therapy (1 month) can achieve radical cure in case of falciparum malaria.

Chloroquine

- It is a synthetic 4-aminoquinoline derivative.
- On oral administration, it is completely and rapidly absorbed from gut. It is concentrated in liver, spleen, kidney and lungs, red blood cells, leucocytes and other tissue proteins. It is slowly excreted by kidney.
- It is a highly effective blood schizonticidal with activity against all 4 species of plasmodia.
- It also has antiamoebic, anti giardial and anti inflammatory actions. In high doses, it depresses myocardium and has a relaxant effect on smooth muscle.
- It also destroys gametocytes of *P. vivax*, *p. ovale* and *P. malariae*, but not of *P. falciparum*.
- It completely cures falciparum malaria.
- Patients become afebrile in 24-48 hours.
- Chloroquine is safe in pregnancy.

Mechanism of action

- Malarial parasites thrive on hemoglobin. Chloroquine acts by interfering with the degradation of hemoglobin by the parasitic
- It concentrates in acidic food vacuoles of the parasite and interferes with the degradation of hemoglobin.
- It also blocks the synthesis of amino acids essential to parasites.

Adverse effects

- Nausea, vomiting, pruritus, headache, visual disturbances, insomnia and skin rashes may occur.
- Prolonged treatment with high doses can cause irreversible retinopathy.
- High doses can also cause cardiomyopathy and psychiatric problems.

Uses

- **Malaria:** Chloroquine is highly effective in the treatment of malaria due to sensitive strains of all 4 species
- **Other uses includes:**
 1. Extraintestinal amebiasis
 2. Rheumatoid arthritis
 3. Photogenic reactions
 4. Leprosy reactions
 5. It is also found to be useful in:
 - Giardiasis
 - Collagen disorder – Rheumatoid arthritis and discoid lupus erythematosus.
 - Infectious mononucleosis

Dose

- Acute attack of malaria – 600 mg (base) is given initially followed after 6 hours by 300 mg, then 150 mg twice daily for next two days. If required it can be given IM or by slow IV injection in a dose of 200-300 mg (base).
- Hydroxychloroquine and amodiaquine have similar pharmacokinetic, pharmacological and adverse effects.

Chemoprophylaxis

It should start 1-2 weeks before going to endemic area, continued throughout the period of stay and for a further period of 6 weeks after return from that area. Drugs used are:

- Chloroquine 300 mg(base) once a week (drug of choice) or pyrimethamine 25 mg per week.
- In chloroquine resistant *P. falciparum* areas, pyrimethamine (25 mg) plus sulphadoxine (500 mg) or sulphamethoxypyridiazine (500 mg).

Quinine

It is an alkaloid which is obtained from cinchona bark. With the invention of safer drugs, it is only used to treat chloroquine resistant strains of *P. falciparum*.

- On oral administration, it is completely absorbed and peak plasma level occurs in 1-3 hours 70% is bound to plasma proteins.
- It is metabolized in the liver and then completely excreted by the kidney within 24 hours. Plasma half-life is 10 hours.
- Quinine is rapidly acting schizonticidal drug and is gametocidal for *P. vivax* and *P. malariae*.
- It is a protoplasmic poison. It may act by inhibiting protein synthesis in the malarial parasites. It destroys erythrocytic forms of the parasites and is useful as a suppressive treatment.
- Quinine also has mild analgesic and antipyretic activity; myocardial depressant and local anaesthetic properties.
- It stimulates uterine muscle during third trimester of pregnancy.

Adverse effects

- Quinine is a gastric irritant and causes, nausea, vomiting and epigastric pain. Cinchonism with ringing in the ears, headache, nausea, visual disturbances and vertigo may be encountered.
- In more severe poisoning, hypoglycemia, fever, delirium, confusion, hypotension, cardiac arrhythmias and coma may develop. Death is due to respiratory arrest.
- It is contraindicated in myasthenia gravis and during pregnancy.

Therapeutic uses

- Used to treat severe (cerebral malaria) and complicated *P. falciparum* malaria resistant to chloroquine by rate controlled IV infusion.
- Used to relieve skeletal muscle spasm in myotonia congenital, a hereditary myopathy.
- Also effective in nocturnal muscle cramps.
- Used as a sclerosing agent in varicose veins.

Mefloquine

- It is a synthetic 4-quinolone methanol derivative. It is a strong schizonticidal drug.
- On oral administration, it is well absorbed and is extensively bound to plasma proteins. It undergoes enterohepatic circulation and has a long half-life of 17 days.
- In a single dose is highly effective against erythrocytic forms of vivax and falciparum malaria: even the multi-drug resistant (MDR) strains of *P. falciparum*.
- It is well-tolerated. Nausea, vomiting, dizziness, confusion, abdominal pain and bradycardia are common. CNS effects like ataxia, disorientation, seizures, encephalopathy and psychotic manifestations are rare and reversible.
- Mefloquine is indicated only in MDR strains of falciparum malaria.
- Mefloquine can also be used in the prophylaxis of multi-drug resistant malaria in travelers.

Halofantrine

It is a phenanthrine methanol derivative.

- It is schizonticidal against erythrocyte forms of all *Plasmodium* species including MDR strains of *P. falciparum*.

Actions are similar to mefloquine but the disadvantages is that the response is unpredictable due to variable absorption: toxicity due to good absorption or therapeutic failure due to poor absorption may result.

Primaquine

It is 8-aminoquinoline derivative.

- On oral administration, it is readily absorbed and is highly concentrated in liver and lungs. It is metabolized in liver and excreted in urine within 24 hours. Its plasma half-life is 3-6 hours.
- It is also effective against persistent tissue phase of *P. vivax* and *P. ovale* and primary exoerythrocytic stage of *P. falciparum*. It is also used as a gametocidal agent in *P. falciparum* malaria.

- Epigastric distress can occur. It may cause hemolysis in patients with G6PD deficiency therefore contraindicated in G6PD deficiency patient.
- Primaquine is used for *radical cure* along with a blood schizonticidal in *P. vivax* and *P. ovale*. Being a toxic drug, it is only used as a radical curative against *P. vivax* malaria after the patient has left the endemic area.
- Primaquine is contraindicated in pregnancy, in patients suffering from rheumatoid arthritis and DLE and in patients receiving hemolytic drugs such as analgesics, sulphonamides, chloramphenicol, nitrofurans and methotrexate.
- Dose – 15 mg/day for 15 days.

Pyrimethamine

It is effective against the erythrocytic forms of all 4 species of plasmodia.

- Being most potent dihydrofolate reductase enzyme inhibitor, it prevents the synthesis of tetrahydrofolate in malarial parasite.
- On oral administration, it is readily absorbed and gets concentrated in kidney, liver, lungs and spleen. It is slowly eliminated.
- It is effective causal prophylactic for *P. falciparum* and *P. vivax*.
- It is an effective blood schizonticidal and gametocidal only to *P. falciparum*.
- When given with sulfoxadine (a sulfonamide), the combination is synergistic and the development of resistance is slower.
- The combination is quite safe and may cause nausea, rashes and in high doses megaloblastic anemia.

Uses1. *Malaria*

	Pyrimethamine (25 mg)	} tab.
a. Acute attacks: +	Sulfadoxine (500 mg)	

combination is used as an alternative in uncomplicated, chloroquine resistant falciparum malaria. It is also used as adjunct to quinine in acute attacks of malaria.

b. *Prophylaxis*: 1-2 tablets once weekly for prophylaxis against MDR falciparum malaria—when a person is visiting an endemic area.

2. *Toxoplasmosis*: Pyrimethamine + Sulfonamide combination is treatment of choice for toxoplasmosis.

Trimethoprim

- It has similar action as that of pyrimethamine but weaker in action.
- It may be used in combination with a sulphonamide, e.g. cotrimoxazole.

Sulfonamide and Sulfones

- They are not effective antimalarial drugs.
- When combined with pyrimethamine, they produce supra-additive synergistic combination due to sequential block.
- The combination is employed for prophylaxis and treatment of chloroquine-resistant malaria.
- The combination should not be used in late pregnancy because of the risk of provoking kernicterus.

Chloroguanide (Proguanil)

It is another dihydrofolate reductase enzyme inhibitor. It is a prodrug. It cyclises and gets converted into triazine cycloguanil.

- It is a schizonticide with causal prophylactic activity against *P. falciparum*.
- It is used for casual prophylaxis of falciparum malaria and as an alternative to pyrimethamine-sulfadoxine for prophylaxis of MDR falciparum malaria.
- It is now rarely used because of two important limitations, i.e.
 - Rapid development of resistant.
 - Slow action

Artemisinin

It is a lactone. It is obtained from Chinese herbal medicine, 'Artemisia annua' Quinghaosu' for almost 2000 years. Its derivative **artemisinin** and related compound **artesunate** (oral and IV preparation) and **artemether** (IM preparation) have undergone clinical trials.

Yinghaosu is also derived from Chinese herb. It is similar in properties to those of quinghaosu.

- It is a potent, rapidly acting, blood schizonticide effective against all the 4 plasmodial species, including MDR *P. falciparum*.
- **Mechanism of action:** It is not known. Most probably they act by damaging cellular membrane of the parasite.
- It is useful in cerebral malaria.
- No resistant strains are known so far. Recrudescence is common due to its short $t_{1/2}$.
- Artesunate (oral, IV) and artemether (IM) are the derivatives used.

- Artemisinin is the best tolerated antimalarial: mild GI symptoms, fever, itching and bradycardia are reported.
- Artemisinin is contraindicated in pregnancy.

Uses

- Acute attacks of MDR falciparum malaria as an alternative to quinine.
- **Dose:** Artesunate, orally 100 mg BD on 1 day, 50 mg BD for next 5 days or IV 120 mg on the first day, 60 mg daily for the next 4 days.

Antibiotics

- **Doxycycline** (100 mg)—It is employed along with chloroquine, quinine or antifolate drugs to treat multidrug resistant malaria. It may be used alone for prophylaxis during stay in endemic areas.
- **Norflaxacin** is effective against chloroquine resistant *P. falciparum* infection.

TREATMENT OF CEREBRAL MALARIA

1. Specific treatment

Quinine dihydrochloride is the drug of choice. 600 mg salt of the drug is diluted with 200-500 ml of 5% glucose solution and infused IV over 2-3 hours. This may be repeated after 8 hours with a maximum dose of 2 gm of the salt in 24 hours.

Alternatively in case of chloroquine sensitive parasites, chloroquine, 200 mg (base) in adults diluted in 5% dextrose and infused over 8 hours, followed by 15 mg/kg which is infused over 24 hours. Parental chloroquine should be avoided in children because it may lead to convulsions and death.

2. Supportive measures

Shock and deep coma:

- Adequate glucose fluid and electrolyte replacement should be given.
- Dexamethasone acetate is given in doses of 8 mg IV followed by 4 mg 8 hourly. After 24 hours, it is tapered off.
- Dopamine is given by IV infusion with constant monitoring of blood pressure.

Convulsions:

- Diazepam is given in doses of 10 mg IV.

Hyperpyrexia:

- Ice sponging.
- Paracetamol 0.5 mg IM 8 hourly or by slow IV infusion with monitoring of blood pressure, with utmost care.

Preferred antimalarial drugs in the treatment and prophylaxis of malaria

Malaria	Drug	Dose, route and duration
<i>Chloroquine sensitive strains</i>		
Treatment	Chloroquine	Oral 600 mg base start, 300 mg after 6 hr 300 mg/day for next 2 days
Prophylaxis	Chloroquine	2 tabs/weeks; start 1 week before and continue for 4 weeks after leaving the endemic area
<i>Chloroquine resistant strains</i>		
Treatment	Choices are: 1. Quinine followed by a. Doxycycline or b. Pyrimethamine + Sulfadoxine 2. Mefloquine 3. Artemisinin (artesunate)	Oral 600 mg TDS for 3 days Severe cases IV 10 mg/kg 8 hourly followed by 100 mg BD for 7 days or [Pyrimethamine 25 mg + Sulfadoxine 500 mg] 3 tab 15 mg/kg single dose (Max 1000 mg) 100 mg BD on first day, 50 mg BD for next 5 days
Prophylaxis	1. Mefloquine 2. Doxycycline	250 mg weekly; start 1 week before and continue for 4 weeks after leaving the area 100 mg weekly; start 2 week before and continue for 4 weeks after leaving the area

Anthelmintics

ANTHELMINTICS

Worm infestation is one of the major global public health problem mostly affecting the tropical and developing countries, where people suffering from worm infestation are in millions. It is seen in people with poor hygiene.

The common parasites are:

Phylum Platyhelminthes Helmints	
Cestodes	Trematodes
<i>Taenia saginata</i> (Beef tapeworm)	Schistosome: <i>S. hematobium</i>
<i>Taenia solium</i> (Pork tapeworm)	<i>S. mansoni</i> and <i>S. japonicum</i>
<i>Diphyllobothrium latum</i> (Fish tapeworm)	Flukes: <i>Fasciola hepatica</i> (Live fluke), <i>Fasciolopsis</i>
<i>Hymenolepis nana</i> (Dwarf tapeworm)	Buski (Giant intestinal fluke), <i>Clonorchis sinensis</i> and <i>Paragonimus westermani</i>
Phylum Nematelminthes Nematodes	
I. Intestinal	II. Somatic
<i>Ascaris lumbricoides</i> (roundworm)	<i>Wuchereria bancrofti</i> (filarial worm),
<i>Ancylostoma duodenal</i> and <i>Necator americanus</i> (hookworm)	<i>Onchocerca volvulus</i> , <i>Loa loa</i>
<i>Enterobius vermicularis</i> (pinworm)	<i>Dracunculus medinensis</i> (guinea worm)
<i>Strongyloides stercoralis</i> (threadworm)	
<i>Trichinella spiralis</i>	

- Worm infestations may causes various symptoms in the host, that includes:
 - GIT abnormality
 - Blood losses (anemia)
 - Nutritional deficiencies.
 - Urticaria and other allergic manifestations.
 - Sometime intestinal and lymphatic obstructions.
- A detailed examination of stool may often spare the unnecessary removal of teeth and tonsils usually blamed for “septic foci”.
- In man, helminthes (worms) infestation is generally limited to the intestinal lumen but in certain situations they can migrate to other tissues.

Definition: A group of compounds used to eradicate parasitic worms form the human body are called **anthelmintic drugs**.

Anthelmintic drugs that kill the worms are known as vermicide while those that expel the worms are called vermifuge. The commonly used drugs are being described individually. Resistance is a rare problem.

CLASSIFICATION

Mebendazole, Piperazine, Albendazole, Livamisole, Teramisole, Thiabendazole, Diethyl Carbamazine Citrate (DEC), Pyrantel pamoate, Niclosamide, Praziquantel Ivermectin.

An ideal anthelmintic should

- Have broader spectrum of action
- Higher efficacy (cure) with preferably single dose
- Not require co-administration of purgative.
- Not get absorbed.
- Free from toxic or adverse effect.
- Palatable and cheap

TREATMENT OF INFESTATIONS CAUSED BY NEMATODES

Nematodes includes (*Ascaris lumbricoides* [round worm] which is the intestinal nematode, filarial and guinea worms which are the blood, lymphatic and other tissues nematodes, hookworms (*Ancylostoma duodenale*), and pin worms (*Enterobius vermiculosis*).

- A group of newly developed drugs (mebendazole, albendazole, pyrantel pamoate, levamisole, tetramisole and thiabendazole) are broad-spectrum anthelmintics.
- These drugs are well tolerated and very effective.
- They do not need preparation of the patients prior to their administration.

Mebendazole

- It is a broad spectrum anthelmintic, discovered in 1972 (congener of thiabendazole)
- It is highly effective in roundworm, hookworm (both species), enterobius and Trichuris infestations. It is also the first drug of choice in treatment of echinococcosis.
- On oral administration, it is poorly absorbed from gut and 90% of the drug is excreted in the feces and 10% is eliminated in the urine unchanged or as metabolites.
- It acts by reversibly impairing glucose uptake in nematodes. It bind with beta tubulin (microtubule protein) of parasite and gradually inhibit them due to this parasite are immobilized and die slowly.
- The eggs and larvae are also destroyed. It is given orally 100 mg twice a day for 3 days. It may be repeated 2-3 weeks later, if needed.
- It is well-tolerated; Allergic reaction, nausea, abdominal pain and diarrhea are seen in heavy infestations. Large doses may cause headache, dizziness, loss of hair and granulocytopenia.
- It may rarely provoke abnormal migration of the roundworms which may come out through mouth or nose.
- It is contraindicated during pregnancy and in children below 2 years of age due to teratogenic and embryotoxic properties.

Uses

- Mebendazole is used in the treatment of *roundworm, hookworm, pinworm, tapeworm, trichuriasis and hydatid disease*.
- It is of special value in multiple worm infestations.

Albendazole

- It is a congener of mebendazole, has actions similar to mebendazole but has advantage of *better tolerability* and its effectivity in a *single dose*.

- On oral administration, it is rapidly absorbed from the gut; metabolized mainly to its sulphoxide, excreted in urine.
- It is an alternative drug to praziquantel in neurocysticercosis (15 mg per kg per 24 hours for one month).
- It should be given carefully in patients with liver or renal disease.
- It is contraindicated in pregnancy.
- Epigastric distress, diarrhea, headache, nausea, dizziness and insomnia are mild side effects.

Therapeutic indications

1. Albendazole is the drug of choice in *roundworm, hookworm, pinworm, trichuriasis infestations* in a single 400 mg dose. Dose to be repeated after 2 weeks in pinworm infestation to prevent reinfection from ova that have matured later.
2. *Trichiniasis, tapeworms and strongyloides* require 3 days treatment.
3. *Neurocysticercosis*: Albendazole is the drug of choice.
4. *Hydatid disease*: Albendazole is the drug of choice; given for 4 weeks.

Thiabendazole

- It is a benzimidazole, acts like mebendazole.
- It is effective against roundworm, hookworm, pinworm, threadworm and whipworm infestations.
- It acts by interfering with the carbohydrate metabolism in the worms and there occurs loss of intracellular microtubules of the worms.
- It also has analgesic, antipyretic, and anti-inflammatory properties which gives total comforting effect to the patient.
- It is the drug of choice for the treatment of threadworm (*Strongyloides stercoralis*) infestation and when *Trichinella spiralis* larvae migrated to skin and skeletal muscle.
- It is given orally in dose of 25 mg per kg twice daily for two days.
- Side effects: Dizziness, anorexia, vomiting, diarrhea, drowsiness, paraesthesia, bradycardia, hypotension, convulsion and liver damage, etc. hallucinations may occur as side effects. Rarely, it may cause Stevens-Johnson syndrome.

Uses: As an alternative to albendazole in strongyloidosis and cutaneous larva migrants

Pyrantel Pamoate

- It is highly effective against roundworm, hookworm and pin worm infestations.

- Pyrantel and its analogues act by causing neuromuscular block. It stimulates the nicotinic cholinergic receptor in the worm leading to persistent depolarization and spastic paralysis (depolarizing neuromuscular blocker) which are then expelled from the gut.
- On oral administration, it is poorly absorbed from the gut and mainly excreted in feces.
- It may cause headache and gastrointestinal discomfort.
- Its recommended dose is 11 mg per kg body weight (single dose)
- It should be used carefully in hepatitis and contraindicated in pregnancy.
- Fasting and purgative are not required with the use of this drug.
- **Side effect:** It is well-tolerated; occasional abdominal pain, headache, rashes, weakness and dizziness may occur.

Uses: In the treatment of roundworm, hookworm and pinworm infestations.

Piperazine Citrate

- It is available as hexahydrate, citrate and phosphate salts.
- Due to large dose and narrow spectrum, it is drug of second choice to treat roundworm and pinworm infestations. A single dose of 4 gm of piperazine hydrate is effective in roundworm infestation while in pinworm infestation a 7 days course (2 gm daily) is required for complete eradication.
- **Mechanism of action:** It competitively blocks the action of acetylcholine and thereby hyperpolarization, i.e. contractions in the worms. Flaccid paralysis results and due to this, the worms are then expelled alive; to facilitate expulsion of the worms often a purgative is given after the drug.
- **Adverse effects:** They are mild-gastrointestinal symptoms; headache and dizziness and muscle in-coordination are seen occasionally.
- **Uses:** Piperazine citrate is indicated for roundworm and pinworm infestations. It is also safe in pregnancy but contraindicated in epilepsy and renal insufficiency.

Levamisole (l-isomer) and Tetramisole (racemic isomer)

- These drugs are used in single doses of 150 mg to treat ascariasis. In case of hookworm infestation,

they are given in two doses of 150 mg at 12 hours interval.

- They cause tonic paralysis by stimulating the ganglia in worms. This helps in expulsion of live worms.
- Levamisole has also been used in rheumatoid arthritis due to its immunosuppressant property.
- They are well-tolerated. However, giddiness and drowsiness may occur rarely. Skin rash, agranulocytosis and proteinuria may occur on prolonged use.

Bephenium (Alcopar)

- It is effective against roundworm and hookworm infestations.
- It is administered in a single dose of 2.5 gm orally.
- Its use has declined as better and less toxic drugs are available.

Diethylcarbamazine (DEC) (Hetrazan)

It is piperazine derivative.

- It is the drug of choice in filariasis. This is highly selective drug against microfilaria and adultworms.
- On oral administration, it is rapidly absorbed, metabolized and excreted in urine.
- It immobilizes the microfilariae resulting in their displacement in the tissues and also alters their surface structure making them more susceptible to the host defense mechanisms. Microfilariae rapidly disappear from the blood except those present in hydrocele and nodules.
- **Adverse effects** mild; anorexia, nausea, vomiting, dizziness and headache; an allergic reaction and fever due to release of antigens from the dying worms may occur.
- Antihistamines are given with DEC to minimize these reactions. DEC can be given during pregnancy.

Uses

1. Filariasis: DEC is the drug of choice (2 mg/kg TDS for 21 days). In 7 days patients are rendered non-infective to mosquitoes as microfilariae rapidly disappear. But adult worms may need repeated courses.
 2. Tropical eosinophilia: (2 mg/kg TDS for 21 days). Symptoms rapidly disappear.
- Preferred drugs for helminthiasis infection: *Look into drugs of choice chapter.*

Ivermectin

- It is the drug of choice in strongyloidosis: It is also useful in the treatment of other forms of filariasis and cutaneous larva migrants.

- It is given in a single dose of 200 μg per kg and produces 60-100% cure.
- Fatigue, dizziness, nausea, vomiting and abdominal pain may occur as side effects.
- It is contraindicated in pregnancy.
- Since ivermectin enhances GABA activity, it potentiates the action of benzodiazepines, barbiturates and related drugs.

TREATMENT OF INFESTATIONS CAUSED BY CESTODES

Taenia saginata, *T. solium* and *Diphyllobothrium latum* are the common cestodes (tapeworms) that infest man. Their life cycle is complex. No symptoms are seen in majority of the patients. However, some patients may suffer from abdominal discomfort, indigestion, anorexia and vitamin B deficiency.

- Drug of choice for tapeworm infestations is niclosamide.

Niclosamide

- It is effective against most tapeworms.
- It acts by affecting the scolex (head) and proximal (tail) segments of the worm through which the worm attaches to the tissue. It produces its effects by inhibiting oxidative phosphorylation in mitochondria and interfering anaerobic generation of ATP by tapeworm. Due to this, the worm is detached from the intestinal wall and ultimately expelled from the body.
- The segments of the dead tapeworms are partly digested and in case of *T. solium*, the ova released from these segments may develop into larvae, reach various organs, specifically lungs, skin and CNS, resulting in visceral cysticercosis. Purge may be given 2 hours after niclosamide to wash off the worms and avoid cysticercosis. The scolex detected in the stool ensures eradication.
- It is administered in a dose of 2 gm orally. To prevent visceral cysticercosis a purgative may be administered. There is no systemic toxicity.

Side effect: Niclosamide is well-tolerated. Abdominal discomfort and rarely pruritus and rashes may occur. The drug can be given safely during pregnancy.

Uses: Niclosamide is the drug of choice in infestations by tapeworms like *T. solium*, *T. saginata*, *H. nana* and *D. latum*. It is also an alternative drug in intestinal fluke infestation.

TREATMENT OF INFESTATIONS CAUSED BY TREMATODES

Trematodes are non-segmented, flattened helminths. Schistosomiasis is the commonest infestation. It is caused by schistosomes (blood flukes) group of trematodes. Following drugs are useful:

Praziquantel

- It is effective against most tapeworms.
- A wide spectrum of cestodes and trematode infestations respond to this drug. It is the first drug which is useful in the treatment of neurocysticercosis.
- On oral administration, it is rapidly absorbed, crosses blood-brain barrier, rapidly metabolized in liver and excreted mostly in urine.
- Abdominal discomfort, headache, dizziness appear as side effects. Its important uses are—
 - 1. Schistosomiasis:** Praziquantel is the drug of choice in all forms of schistosomiasis.
 - 2. Neurocysticercosis:** Praziquantel is an alternative to albendazole.
 - 3. Tapeworms:** Single dose (10 mg/kg) of praziquantel is effective in all tapeworm infestations. In *T. solium* it has the advantage that it kills the larvae and therefore visceral cysticercosis is avoided.

Bithinol

It is given orally in a dose of 40-50 mg per kg every other day for up to 15 doses.

Oxaminiquine

To treat schistosomiasis, it is administered in a dose of 12-15 mg per kg orally.

Niridazole

To treat schistosomiasis, it is given in a dose of 25 mg per kg daily in divided doses for 7 days. It may cause headache, gastrointestinal disturbances, insomnia and psychiatric disturbances.

Antimony potassium tartrate

To treat all the three species of schistosomiasis infestation, it is given intravenously in a dose of 8 ml of 0.5% solution; gradually dose is increased every day up to 360 ml of the solution. It is contraindicated in cardiac, hepatic and renal insufficiency.

Drugs for Trypanosomiasis and Leishmaniasis

LEISHMANIASIS

- The infection is transmitted by the bite of the (vector) female sandfly phlebotomies.
- Leishmaniasis is caused by protozoa of the genus leishmania while
- Kala-azar or visceral leishmaniasis is caused by *Leishmania donovani*;
- Oriental sore by *L. tropica* and mucocutaneous leishmaniasis by *L. braziliensis*.
- It is endemic in Bihar.

Classification of drugs used in leishmaniasis include:

Antimony compounds	<i>Sodium stibogluconate, Diamidines, Pentamidine, isethionate</i>
Other drugs	<i>Amphotericin B, Ketoconazole, Allopurinol, Paramomycin</i>

Sodium Stibogluconate

- This pentavalent antimonial is the most effective drug in kala azar (drug of choice)
- It is also effective in mucocutaneous and cutaneous leishmaniasis.
- It is given as a 4% solution in the dose of 10-20 mg/ kg IM (gluteal region) or IV for 20 days.

Mechanism of action: Unknown.

Adverse effects

- These include a metallic taste in the mouth, nausea, vomiting, diarrhea, headache, myalgia, arthralgia, pain at the injection site, bradycardia, skin rashes, hematuria and jaundice.
- Sometimes sudden death due to shock have occurred.
- ECG should be monitored as arrhythmias can occur during the later days of therapy.

- Resistance may develop specially in endemic areas like Bihar.

Meglumine antimonate and **ethyl stibamine** can also be used in all forms of leishmaniasis.

Pentamidine Isethionate

- It is an aromatic diamidine effective against *Leishmania donovani*, trypanosomes, *Pneumocystis carinii* and some fungi.
- If given intramuscularly, the drug is rapidly absorbed but CNS level (concentration) remains lower. Dose 4 mg / kg deep IM or slow IV on alternate days for 5-25 weeks.
- **Adverse effects:** Pentamidine liberates histamine which is responsible for vomiting, diarrhea, flushing, pruritis, rashes, tachycardia and hypotension apart from pain at the injection side . Other effects include hepatotoxicity, renal impairment, ECG changes and in some patients diabetes mellitus may be precipitated.

Uses

- 1. Leishmaniasis:** Pentamidine can be used for the treatment of visceral leishmaniasis as an alternative to sodium stibogluconate.
- 2. Pneumocystis carinii infections:** Pentamidine is an alternative in pneumocystis carinii infections in patients unable to tolerate cotrimoxazole.
- 3. Trypanosomiasis (sleeping sickness)** pentamidine can be used as an alternative to suramin in trypanosomiasis. It can also be used for chemoprophylaxis against African trypanosomiasis.

Other Drugs

Amphotericin B

- It is employed in cases of kala azar not responding to antimonials and pentamidines. It is given in doses of

5-10 mg, gradually increased by 5-10 mg each day, till a dose of 0.5 mg per kg body weight is reached. Then given on alternate days till a total of 1-3 gm is reached.

Ketoconazole

- It inhibits ergosterol synthesis in the leishmania and is effective in cutaneous leishmaniasis.
- It is used to treat resistant kala-azar and dermal leishmaniasis in dose of 200 mg thrice daily for 4 weeks.

Allopurinol

- In leishmaniasis, allopurinol is converted to a metabolite which inhibits protein synthesis. It may be used along with antimonials.
- Doses: 300 mg 3-4 times a day for 2-4 weeks.

Paramomycin (Aminosidine)

- It is an amoebicidal drug which is also found to be effective in leishmaniasis.
- It is useful in all forms of leishmaniasis. It can be used alone or in combination with antimonials.

TRYPANOSOMIASIS

- Trypanosomiasis is caused by protozoa of the genus *Trypanosoma*. African trypanosomiasis or sleeping sickness is caused by *T. gambiense* and *T. rhodesiense* while South American trypanosomiasis is caused by *T. cruzi*.

- Drugs used in trypanosomiasis are *suramin*, *pentamidine*, *melarsoprol*, *eflornithine*, *nifurtimox* and *benznidazole*.

Melarsoprol

- It is the preferred drug in later stages of trypanomiasis which is associated with encephalitis and meningitis.

Suramin sodium

- It is the drug of choice for early stage of trypano-somiasis but it does not cross the BBB and therefore cannot be used in later stages of the diseases.
- It is also useful for the prophylaxis but pentamidine is preferable.
- Suramin is given IV; it is extensively bound to plasma proteins and may be traced for nearly months in the plasma.
- Suramin is also effective in eradicating adult forms of *onchocerca volvulus*.
- **Toxicity** is high; vomiting, shock and loss of consciousness may follow IV injections. Rash, neuropathies, hemolytic anemia and agranulocytosis may also occur.

Eflornithine

- It is used as an alternative in CNS trypanomiasis.
- **Nifurtimox** and benznidazole are useful in Chaga's disease (American trypanosomiasis).

Immunostimulants and Immunosuppressants

IMMUNOSTIMULANTS

- There are certain agents or compounds which are used for enhancing the immunological and nonspecific host defense. These agents modulate the immune response and can be used to increase the immune responsiveness of patients with immunodeficiency as in AIDS, chronic illness and cancers.

Immunostimulant may act by:

- Enhancing humoral antibody response.
- Enhancing macrophageal (phagocytic) activity.
- Modifying the cell mediated immune response.

This is still a developing field of pharmacology. The drugs currently used for this purpose are:

- Human Interferon's:** They are the cytokines produced by host cells in response to viral infections. There are three types, i.e. α , β , and γ interferon's in man. They also have immunomodulating and antiproliferative properties. They inhibit the multiplication of many DNA and RNA viruses.
- Amantadine
- Tilorane
- BCG has been tried in cancers.
- Levamisole used in helminthiasis is also found to enhance cell-mediated immunity in humans. It acts by modulating cell mediated immune response. It has been tried in some cancers.
- Clofazimine: Just like BCG vaccine, it also enhances phagocytic activity of macrophages.

IMMUNOSUPPRESSANTS

Any drug or agent which are used to suppress immunological host defense, i.e. inhibit immunity, suppresses cell mediated or humoral immunity or both.

Immunosuppressant can be classified by various ways:

- Agents which act by general suppression of all immune response, e.g. cytotoxic drugs.
- Those which are specific suppressants of immune response, i.e. antilymphocytic serum (ALS), cyclosporine and OKT₃.
- Those which reduce the unwanted reactions due to immune responses, probably by its anti-inflammatory actions, i.e. corticosteroids, phenylbutazone.

Classification

1. T-cell inhibitors	Cyclosporine, tacrolimus
2. Cytotoxic drugs	Methotrexate, Azathioprine, Cyclophosphamide
3. Adrenocorticosteroids	Chlorambucil
4. Antibody reagents.	

Cyclosporine

It is a cyclic peptide produced by a fungus.

- Actions:** Cyclosporine acts at an early stage and selectively inhibits T cell-proliferation. It also inhibits interleukin 2-production.
- Thus cyclosporine selectively suppresses cell mediated immunity but not humoral immunity.

Uses

- In organ transplantation:** Cyclosporine is very effective for the prophylaxis and treatment of graft rejection in organ transplantation surgeries; *like kidney, liver, bone marrow and other transplants.*
- Autoimmune disorders:** Cyclosporine is also useful in some autoimmune disorders like rheumatoid arthritis.

Adverse effects

They include nephrotoxicity, hepatotoxicity, anorexia, gum hypertrophy and increased susceptibility to infections.

Cytotoxic Drugs

- Cyclophosphamide and methotrexate inhibit cell-mediated immunity like azathioprine, (while cyclophosphamide predominantly suppresses humoral immunity).
- They are used in the prevention of graft rejection and in autoimmune disorders.

Glucocorticoids

- They have potent immunosuppressant activity and are used in the prevention of organ transplant rejection and in autoimmune disorders.

ANTIBODIES AS IMMUNOSUPPRESSANTS**Muromonab CD3**

- It is a monoclonal antibody to CD3 antigens on T lymphocytes.
- On intravenous administration, T cells disappear from the circulation within minutes.
- It is used with other immunosuppressants in organ transplantation. Fever, chills and pulmonary edema may occur.

Antithymocyte Globulin (ATG)

- It binds with T lymphocytes and deplete them thereby suppressing immune response.
- It is used in the management of organ transplantation.

Drugs of Choice

Gram-positive cocci	Diseases	Sensitivity	Drug of 1st choice	Alternative drugs
<i>Staphylococcus aureus</i>	Abscesses Bacteremia Cellulitis Endocarditis Osteomyelitis Pneumonia Other	Penicillin sensitive	Penicillin	
		Methicillin-sensitive	Nafcillin or oxacillin	A cephalosporin (G1) Vancomycin Cotrimoxazole+ Rifampicin
		Methicillin-resistant	Vancomycin	Linezolid, cotrimoxazole, Minocycline, tigecycline
<i>Streptococcus pyogenes</i> (Group A)	Bacteremia Cellulitis Erysipelas Other systemic infection Otitis media, sinusitis Pharyngitis Pneumonia Scarlet fever Toxic shock- Like syndrome		Penicillin Amoxicillin Clindamycin	A cephalosporin (G1) Vancomycin Quinolones Macrolides
<i>Streptococcus</i> (viridans group)	Bacteremia Endocarditis		penicillin G ± Aminoglycosides	cephalosporin (G1, 3) ceftriaxone Vancomycin
<i>Streptococcus agalactiae</i> (group B)	Bacteremia Endocarditis		Ampicillin or penicillin G ± an aminoglycoside	A cephalosporin (G1) Vancomycin
	Meningitis		Ampicillin or penicillin G ± an aminoglycoside	Ceftriaxone or cefotaxime
<i>Streptococcus boyis</i>	Bacteremia Endocarditis		See viridans streptococci	

- G1 – First Generation
- G2 – Second Generation
- G3 – Third Generation

Contd...

Contd...

Gram-positive cocci	Diseases	Sensitivity	Drug of 1st choice	Alternative drugs
<i>Streptococcus</i> (anaerobic species)	Bacteremia Brain and other abscesses Endocarditis Sinusitis		Penicillin G	A cephalosporin (G1) Clindamycin Vancomycin
<i>Streptococcus pneumoniae</i> (Pneumococcus)	Arthritis Otitis Pneumonia sinusitis	Penicillin-sensitive	Penicillin Amoxicillin	A cephalosporin (G1) Cotrimoxazole Macrolid Clindamycin
		Penicillin-resistant	Ceftriaxone or cefotaxime Vancomycin	Clindamycin FQ Cotrimoxazole
	Endocarditis Meningitis Other serious Infection	Penicillin-sensitive	Penicillin	Ceftriaxone or cefotaxime Vancomycin
		Penicillin-intermediately resistant	Cefotaxime or ceftriaxone	
		Penicillin G-resistant	Vancomycin + Rifampicin Cefotaxime or cefotaxime	Cefotaxime or Cefotaxime Chloramphenicol Vancomycin
<i>Enterococcus</i>	Endocarditis or other serious infection (bacteremia)		Penicillin G + Gentamicin or ampicillin	Linezolid chloramphenicol
	Urinary tract infection		Amoxicillin or ampicillin or penicillin	Vancomycin, FQ Ciprofloxacin Chloramphenicol
Gram-negative cocci				
<i>Moraxella catarrhalis</i>	Otitis Pneumonia Sinusitis		Amoxicillin + clavulanate Ampicillin + sulbactam Cotrimoxazole	A cephalosporin (G2 or G3) Ciprofloxacin Tetracycline, Erythromycin
<i>Neisseria gonorrhoeae</i> (gonococcus)	Urithritis cervivitis	Penicillin-sensitive	Penicillin G Ampicillin probenecid or amoxicillin	Cefriaxone, cefixime, or cefoxitin Doxycycline
		Penicillin-resistant	Cefpodoxime Cefriaxone or cefixime spectinomycin	cefoxitin
<i>Neisseria meningitides</i> (meningococcus)	meningitis carrier state (post-treatment)		Penicillin G Rifampin	Ceftriaxone or cefataxime Ciprofloxacin, Minocycline
Gram-positive bacilli				
<i>Bacillus anthracis</i>	Malignant pustule Pneumonia		Penicillin G	Erythromycin Doxycycline Cephalosporin (G1) Chloramphenicol

• FQ = Fluoroquinolones; G1, G2, G3 [First, Second and Third Generation]

Contd...

Contd...

Gram-positive bacilli	Diseases	Drug of 1st choice	Alternative drugs
<i>Corynebacterium diphtheriae</i>	Laryngotracheitis Other local lesions Pharyngitis Pneumonia Carrier state	Macrolids	Clindamycine Cephalosporine (GI) Rifampicin
<i>Corynebacterium</i> species aerobic and anaerobic (diphtheroids)	Bacteremia Endocarditis Infected foreign bodies	Macrolids Penicillin G ± an Aminoglycoside Vancomycin	Rifampicin + penicillin G Ampicillin-sulbactam
<i>Listeria monocytogenes</i>	Meningitis	Ampicillin or Penicillin-G ± Gentamycine	Cotrimoxazole
	Bacteremia	Ampicillin or penicillin G + Gentamicin	Cotrimoxazole Chloramphenicol
<i>Erysipelothrix rhusiopathiae</i>	Erysipeloid	Penicillin G	Erythromycin Doxycycline Chloramphenicol
<i>Clostridium perfringens</i> and other species	Gas gangrene	penicillin G	Cefoxitin, Ceftizoxime Clindamycin Doxycycline
<i>Clostridium tetani</i>	Tetanus	Penicillin G Vancomycin	Clindamycin Doxycycline
<i>Clostridium difficile</i>	Antibiotic-associated colitis	metronidazole (oral)	Vancomycin (oral)
Gram-negative bacilli			
<i>Escherichia coli</i>	Urinary tract infection	Cotrimoxazole Ciprofloxacin or ofloxacin A cephalosporin (GI)	Penicillin An aminoglycoside
<i>Escherichia coli</i>	Bacteremia Other infections	Ampicillin, an Aminoglycoside or levofloxacin A cephalosporin (GI)	A penicillin, Aztreonam
<i>Enterobacter species</i>	Urinary tract and other infections	Imipenem An aminoglycoside cotrimoxazole	Cefepime, A broad-spectrum penicillin
<i>Proteus mirabilis</i>	Urinary tract and other infections	Ampicillin or amoxicillin	A cephalosporin Ciprofloxacin
<i>Proteus</i> , other species	Urinary tract and other infections	Ciprofloxacin A cephalosporin (G3)	An aminoglycoside A penicillin + a beta-lactamase inhibitor Aztreonam, imipenem
<i>Pseudomonas aeruginosa</i>	Urinary tract and other infections	A broad-spectrum penicillin Ceftazidime or cefepime Ciprofloxacin or ofloxacin	Tobramycin Aztreonam
	Bacteremia pneumonia	A broad-spectrum penicillin + tobramycin Ceftazidime or cefepime + tobramycin	Ciprofloxacin + a broad spectrum penicillin Tobramycin Aztreonam

Contd...

Contd...

Gram-negative bacilli	Diseases	Drug of 1st choice	Alternative drugs
<i>Klebsiella pneumoniae</i>	Urinary tract infection	A cephalosporin	An aminoglycoside Mezlocillin or piperacillin
	Pneumonia	A cephalosporin or an aminoglycoside	Ciprofloxacin Aztreonam or Imipenem cotrimoxazole Ampicillin
<i>Salmonella</i>	Bacteremia Paratyphoid fever Typhoid fever Acute gastroenteritis	Ciprofloxacin or ofloxacin ceftriaxone	Cotrimoxazole or ampicilline
<i>Shigella</i>	Acute gastroenteritis	Norfloxacin or ciprofloxacin	Cotrimoxazole or Ampicilline Aztreonam
<i>Serratia</i>	Variety of nosocomial and opportunistic infections	Imipenem Cefoxitin, cefotetan	Third-generation Cephalosporin
<i>Acinetobacter</i>	Various nosocomial infections	Imipenem An aminoglycoside	A cephalosporin (G3) Cotrimoxazole
<i>Hemophilus influenzae</i>	Otitis media Pneumonia sinusitis Epiglottitis Meningitis	Cotrimoxazole Amoxicillin-clavulanate Cefuroxime, axetil Ceftriaxone or cefotaxime Chloramphenicol	Amoxicillin or Ampicillin Cotrimoxazole Ampicillin-sulbactam
<i>Hemophilus ducreyi</i>	chancroid	Ceftriaxone Cotrimoxazole, Macrolide	Ciprofloxacin Doxycycline
<i>Brucella</i>	Brucellosis	Doxycycline + gentamicin Doxycycline + rifampin Trimethoprim + rifampin	cotrimoxazole + gentamicin
<i>Yersinia pestis</i>	Plague	Streptomycin ± a tetracycline	Doxycycline Ciprofloxacin Chloramphenicol
<i>Yersinia enterocolitica</i>	Yersiniosis	Cotrimoxazole	A cephalosporin (G3) Ciprofloxacin or ofloxacin
	Sepsis	An aminoglycoside chloramphenicol	
<i>Francisella tularensis</i>	Tularemia	Streptomycin or gentamicin	Doxycycline Ciprofloxacin Chloramphenicol
<i>Pasteurella multocida</i>	Abscesses Bacteremia Meningitis Wound infection (animal bites)	Amoxicillin-Clavulanate Penicillin G	Doxycycline Ceftriaxone
<i>Vibrio cholerae</i>	Cholera	Doxycycline Ciprofloxacin or ofloxacin Vancomycin	Cotrimoxazole Cotrimoxazole Rifampin
<i>Flavobacterium meningosepticum</i>	Meningitis		
<i>Pseudomonas mallei</i>	Glanders	Strptomycin + a tetracycline	Streptomycin + Chloramphenicol
<i>Pseudomonas pseudomallei</i>	Melioidosis	Ceftazidime or ceftriaxone Cotrimoxazole	Imipenem Chloramphenicol

Contd...

Contd...

Gram-negative bacilli	Diseases	Drug of 1st choice	Alternative drugs
<i>Campylobacter jejuni</i>	Enteritis	Ciprofloxacin or ofloxacin	A macrolid or clindamycin
<i>Campylobacter fetus</i>	Bacteremia Endocarditis Meningitis	Gentamicin Ampicillin Ampicillin	Ceftriaxone Imipenem Ceftriaxone
<i>Fusobacterium nucleatum</i>	Genital infections Gingivitis Lung abscess, empyema Ulcerative pharyngitis	Penicillin G Clindamycin	Metronidazole A cephalosporin (G1) Doxycycline
<i>Calymmatobacterium granulomatis</i>	Granuloma inguinale	Doxycycline	Cotrimoxazole
<i>Streptobacillus moniliformis</i>	Abscesses Arthritis Bacteremia Endocarditis	Penicillin G	Streptomycin Doxycycline Macrolide Chloramphenicol
<i>Legionella pneumophila</i>	Legionnaires' disease clarithromycin cotrimoxazole doxycycline	Azithromycin A fluoroquinolones	Ciprofloxacin or Clarithromycin Cotrimoxazole Doxycycline
Acid fast bacilli			
<i>Mycobacterium avium-intracellulare</i>	Disseminated disease in AIDS	Clarithromycin Ethambutol	Rifabutin Ciprofloxacin Amikacin
<i>Mycobacterium tuberculosis</i>	Pulmonary military, renal, meningeal, and other tuberculous infections	Ispmoazod + rifampin + pyrazinamide + ethambutol	isoniazid + rifampin + ethambutol
<i>Mycobacterium leprae</i>	Leprosy	Dapsone + rifampin + clofazimine	Clofazimine Ofloxacin
Spirochetes			
<i>Treponema pallidum</i>	Syphilis	Penicillin G	Doxycycline or ceftriaxone
<i>Treponema pertenue</i>	Yaws	Penicillin G Streptomycin	Doxycycline
<i>Borrelia burgdorferi</i> (Lyme disease)	Erythema chronica migrans-skin Stage 2-neurological, cardiac, arthritis	Doxycycline Ceftriaxone	Amoxicillin, Ceftriaxone Azithromycin Penicillin G Tetracycline
<i>Borrelia recurrentis</i>	Relapsing fever	Doxycycline	Erythromycin penicillin G
<i>Leptospira</i>	Weil's disease Meningitis	Penicillin G	Doxycycline
Actinomycetes			
<i>Actinomyces israelii</i>	Abdominal, cervicofacial, horacic, and other lesions	Penicillin G Ampicillin	Doxycycline Macrolides

Contd...

Contd...

Actinomycetes	Diseases	Drug of 1st choice	Alternative drugs
<i>Nocardia asteroides</i>	Brain abscess Lesions of other organs Pulmonary lesions	Clotrimoxazole A sulfonamide	Minocycline Imipenems, amikacin
Miscellaneous agents			
<i>Ureaplasma urealyticum</i>	Nonspecific urethritis	Doxycycline	Macrolide
<i>Mycoplasma pneumoniae</i>	“Atypical pneumonia”	Doxycycline	Azithromycin or clarithromycin
<i>Rickettsia</i>	Brill’s disease Murine typhus, Typhus fever Q fever Rickettsialpox rocky Mountain spotted fever	Doxycycline	Chloramphenicol
<i>Chlamydia psittaci</i>	Psittacosis (ornithosis)	Doxycycline	Chloramphenicol
<i>Chlamydia trachomatis</i>	Lymphogranuloma venereum	Doxycycline	Clotrimoxazole Azithromycin
	Trachoma	Azithromycin	Doxycycline
Microbes			
	Inclusion conjunctivitis (blennorrhea) Nonspecific urethritis cervicitis	Azithromycin Azithromycin	Doxycycline Doxycycline Amoxicilline
<i>Chlamydia pneumoniae</i>	Pneumonia	Doxycycline Azithromycin Clarithromycin	A fluoroquinolone
<i>Pneumocystis carinii</i>	Pneumonia in impaired host	Mild or moderate disease Moderately severe or severe disease	Clotrimoxazole Trimethoprim sulfamethoxazole
			Trimethoprim-dapsone Clindamycin-primaquin
Fungi			
<i>Candida species</i>	Cutaneous or vaginal thrush	Fluconazole Nystatin	Itraconazole Ketoconazole
	Oral thrush	Fluconazole Clotrimazole Nystatin	
	Deep infection	Amphotericin B ± Flucytosine	
<i>Coccidioides immitis</i>	Disseminated (nonmeningeal)	Amphotericin B	Fluconazole or itraconazole
	Meningitis	Amphotericin B Fluconazole	Itraconazole
<i>Histoplasma capsulatum</i>	Chronic pulmonary disease	Itraconazole, Ketoconazole	Amphotericin B Fluconazole
	Disseminated	Amphotericin B	Itraconazole
<i>Blastomyces dermatitidis</i>	All	itraconazole	Amphotericin B

Contd...

Contd...

Fungi	Diseases	Drug of 1st choice	Alternative drugs
<i>Paracoccidioides brasiliensis</i>	All	Itraconazole	Amphotericin B followed by a sulfonamide
<i>Sporothrix schenckii</i>	Cutaneous	Iodide	Itraconazole
	Extracutaneous	Amphotericin B (Liposomal)	Itraconazole
<i>Aspergillus species</i>	Invasive	Amphotericin B	Itraconazole
Agents of mucormycosis	All	Amphotericin B	
<i>Cryptococcus neoformans</i>	Pulmonary (nonmeningeal)	Amphotericin B	
	Meningitis	Amphotericin B ± Fucytosine	Fluconazole
Viruses			
Herpes simplex virus	Genital disease Keratoconjunctivitis Encephalitis Neonatal HSV Mucocutaneous HSV in immuno-compromized host	Acyclovir Trifuridine Acyclovir Acyclovir Acyclovir	– Acyclovir – – Foscarnet
Varicella zoster virus	Herpes zoster or varicella in immuno-compromized host, pregnancy Varicella or herpes zoster in normal host	Acyclovir Acyclovir Famciclovir Valacyclovir Ganciclovir	Foscarnet Acyclovir
Cytomegalovirus	Retinitis in patients with AIDS		Foscarnet
Human immunodeficiency virus	AIDS HIV antibody positive and CD4 count less than 500/mm ³	2 NRTIs + PI	2 NRTIs + NNRTI 2 NRTIs + NNRTI + PI
Influenza A	Influenza	Rimantadine	Amantadine Zanamivir Oseltamivir
Respiratory syncytial virus	Pneumonia and bronchiolitis of infancy	Ribavirin (aerosol)	
Human papilloma virus	Genital papilloma	Interferon Alfa	–
Hepatitis B virus	Chronic hepatitis B	Interferon alfa-2b	Lamivudine adefovir entecavir
Hepatitis C virus	Acute hepatitis C virus Chronic hepatitis C virus	Interferon alfa-2b Interferon alfa-2a Interferon alfa-2b	– Pegylated interferon alfa-2a Pegylated interferon alfa-2b Ribavirin

- NRTI: Nucleoside Reverse Transcriptase Inhibitor
- PI – Protease Inhibitors
- NNRTI – Non-nucleoside Reverse Transcriptase Inhibitor



S E C T I O N

13

Cancer Chemotherapy

Cancer Chemotherapy

CANCER

Basically cancer is a disease of cells characterized by:

1. Uncontrolled growth of abnormal cells, not regulated by external signals, usually resulting in the formation of a tumor.
2. Ability of the growing cells to invade surrounding tissue, spread to new sites and establish new growths – metastasize at distant sites.
 - A neoplasm is **benign**, if only the first feature is present and
 - It is **malignant** if the second feature is also present.
 - Cancers of epithelial tissues are called **carcinomas** and
 - Cancers of non-epithelial tissues (mesenchymal) are called **sarcomas**.
3. Cancer is one of the major causes of death in world.
4. The treatment of cancer is still unsatisfactory due to certain characteristics of the cancer cells—like capacity for uncontrolled proliferation, invasiveness and metastasis.
5. The cancer cells are our own cells, not like microbes which means that, drugs which, destroy these cells can also affect normal cells.
6. The host defense mechanisms which help us in infections is not doing so in cancers as these cancer cells are also host cells.
7. Moreover, the cancer cells can be in a resting phase during which they are not sensitive to anticancer drugs but can start multiplying later—resulting in recurrence. These features have made cancer chemotherapy more difficult.

The abnormal behavior of the cancer cells leads to illness in the host as a result of:

1. Pressure effects of the local tumor growth.
2. Destruction of the organ involved by the primary growth or its metastases.
3. Systemic effects as a result of new growth.

Six different modes, either used alone, sequentially or concurrently are employed in the therapy of cancer:

1. Chemotherapy (Cytotoxic drug therapy or chemotherapy)
2. Surgery
3. Radiotherapy
4. Endocrine therapy
5. Immunotherapy and biological therapy
6. Gene therapy.

Cytotoxic drug therapy (chemotherapy) is employed in cancer to:

1. Eradicate the disease.
2. Control symptoms of the disease. In this context cytotoxic drugs may be used
 - a. After surgery or radiotherapy as adjuvant chemotherapy.
 - b. Together with surgery or radiotherapy as palliative therapy.
 - c. Alone, as symptomatic therapy for controlling local physical effects of a tumor mass.

The main problem with chemotherapy of cancer is that:

- In chemotherapy of infections, the invading microbes are biologically foreign to the host and the metabolic reactions of its cells are so different from those of the host tissues that a chemotherapeutic agent can attack them selectively without affecting the host tissue cells. No such clear cut difference can be demonstrated between cancer and normal cells, as a result the anticancer drugs lack the specificity of antimicrobial drugs and have a much lower margin of safety. These

drugs, therefore, not only act on the cancer cells but also attack dividing normal cells of the bone marrow, gastrointestinal tract, lymphoid tissue, hair follicles and spermatogenic cells, resulting in a large number of side effects.

- In infections, the body helps the antimicrobial drug with its own defense mechanism in the form of antibody production, phagocytosis, etc. in the eradication of the causative organism. Such defense mechanism is usually lacking or ineffective in cancer. It is, therefore, necessary to give anticancer drugs in such doses, so as to destroy all the cancer cells. Due to lack of selectivity of anticancer drugs, it is often impracticable to use such large doses. Hence, even after satisfactory initial treatment, the possibility of recurrence remain always there.
- Neoplastic tissue can develop resistance to drugs.

CLASSIFICATION OF DRUGS USED IN MALIGNANCY

Cell cycle nonspecific drugs

1. Alkylating agents

- a. Mechlorethamine-cyclophosphamide (causes alopecia), melphalan, chlorambucil.
- b. Nitrosoureas-highly lipid soluble can cross blood-brain barrier, useful in brain tumors-carmustine, lomustine, semustine.
- c. Miscellaneous: Thiotepa-(ovarian cancer), busulfan-(chronic myeloid leukemia) cisplatin-(oral and genitourinary cancer), procarbazine.

2. **Antibiotics:** Anthracyclines-doxorubicin, daunorubicin-broad spectrum, useful in many cancers, cardiotoxic, causes total alopecia. Plicamycin-used to reverse hypercalcemia associated with malignant disease. Mitomycin-used for topical and intravesical treatment of small, bladder papillomas.

Cell-cycle specific drugs

1. Antimetabolites-all used in combination with allopurinol to avoid occurrence of Hyperurecemia.
 - a. [Dihydrofolate reductase (DHF Rase) inhibitor]-methotrexate-also used in psoriasis, Rheumatoid arthritis.
 - b. Pyrimidine antagonists-cytarabine, fluorouracil.
 - c. Purine antagonists-mercaptopurine, thioguanine, gemcitabine-pancreatic cancer, capecitabine.
2. Bleomycin-causes pulmonary fibrosis, does not have significant myelosuppressive effect.
3. Plant alkaloids: prodophytotoxins, vincristine, vinblastine, paclitaxel; all these bind to microtubular proteins

and cause depolymerization of microtubules, resulting in mitotic arrest at metaphase, dissolution of the mitotic spindle and interference with chromosome segregation.

Hormonal agents

1. Glucocorticoids-**prednisolone**-used mainly in hematological cancers-acute leukemia, lymphoma.
2. Estrogen and androgen inhibitors-**tamoxifen**-post menopausal breast cancer. **Flutamide**-prostatic cancer.
3. Gonadotrophins-releasing hormone agonist-antagonists-**leuprolide**, **goserelin**-initial stimulation followed by prolonged inhibition of FSH and LH-metastatic prostate carcinoma.
4. Aromatase inhibitors-aminoglutethimide, anastrozole-both prevent conversion of adrenal androgen to estrone. Aminoglutethimide prevents synthesis of steroids-conversion of cholesterol to pregnenolone. Given with hydrocortisone. Used as second line drugs for metastatic breast cancer.

Immunotherapy

1. Active non-specific immune stimulation-BCG vaccine.
2. Active specific immune stimulation-C-Vax melanoma cell vaccine.
3. Immunomodulators-Levamisole.
4. Cytotoxic Cytokines-Interferon-alpha (α).
5. Immunostimulatory cytokines-IL-2.
6. Adaptive cellular immunotherapy-LAK cells, TIL, antigen-pulsed dendritic cells.
7. Monoclonal antibodies-anti-CEA, CD20, HER-2, ECF, Mabs. (Monoclonal antibodies)

Cell cycle and anticancer drugs: Cellular multiplication involves the passage of the cells through a cycle called cell cycle. The various phases of cell cycle are:

1. After mitosis, some of the daughter cells pass into resting phase or non proliferative phase G_0 phase and do not enter the cell-cycle phase G_1 , immediately.
2. The interval following cell division to the point where DNA synthesis starts again, is known as presynthetic phase or **G_1 phase**.
3. This is followed by a phase during which synthesis of DNA occurs called the **S phase**.
4. This is then followed by premitotic or post DNA synthetic phase called **G_2 phase**.
5. This is followed by mitotic or **M phase**, during which the chromosomes separate into two daughter cells. These

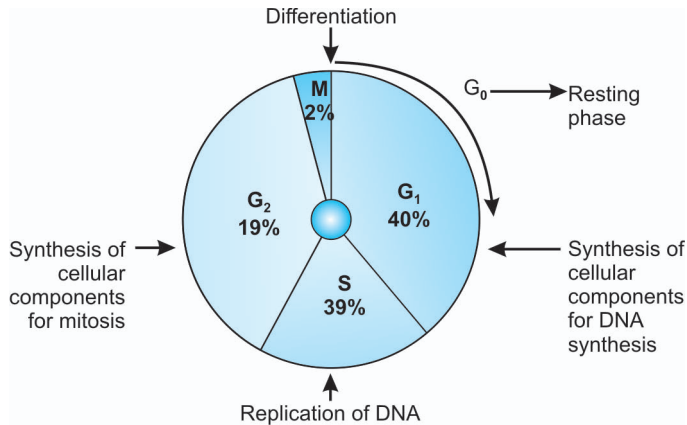


Fig. 13.1.1: Phases of cell cycle

daughter cells have the option of either entering the G₁ phase or remain in the **G₀ phase**. See Fig. 13.1.1.

Most of the anticancer drugs act specifically on the processes like DNA synthesis, transcription or the mitotic phase and are called – **cell cycle phase specific drugs**. These drugs do not act on the cells in **G₀ phase**. Some drugs kill the cells during all or most of the phases of cell cycle including **G₀ phase** and are therefore, **called cell cycle phase non-specific drugs**.

Phase specific drugs or schedule dependent drugs

1. Antimetabolites – methotrexate, 6-mercaptopurine (6-MP), 5-fluorouracil (5-FU), cytarabine – act on the **S phase**.
2. Hormones – prednisolone – act on the **G₁ phase**.
3. Natural products – vincristine, vinblastin, vindesine, asparaginase – act on **M phase**. Paclitaxel, docetaxel.
4. Miscellaneous – procarbazine, hydroxyurea.

Phase nonspecific drugs or dose dependent drugs

1. Alkylating agents: Nitrogen mustard, carmustine, busulphan, chlorambucil, cyclophosphamide, cisplatin.
2. Antibiotics: Bleomycin, dactinomycin, doxorubicin, daunorubicin, mitomycin C.

Mode of action of drugs (Fig. 13.1.2)

1. **Alkylating agents:** They act by transferring alkyl groups to DNA during cell division, resulting in DNA strand breakage or cross linking of the two strands, so that normal synthesis of DNA is prevented.
2. **Antimetabolites:** These are synthetic analogues of normal metabolites and act as competitive antagonists of folic acid – methotrexate, purines.

Principles of drug therapy: The common anti-cancer practice is to use a combination of two to six drugs, which are given simultaneously or closely related in time. Combination of drugs is more effective than single agents and is achieved by:

- Combining drugs, which are active alone and have different mechanisms of action.
- Combining drugs with different toxicities.

Cytotoxic drugs are given in intermittent regimens. Pulses of drug or drug combination are given at 3-4 weeks intervals, in maximum tolerated doses, thus increasing the effectiveness and reducing the toxicity of the combination and providing adequate time for recovery of the normal cellular elements depressed by the drugs. Usually, phase non-specific drugs are employed first, followed by phase specific agents. The former reduces the non-proliferative cell pool (G₀) which stimulates the survivors to enter multiplication phase, where they are killed, by using phase specific drugs.

In addition to oral and IV routes cytotoxic drugs can also be given intrathecally to achieve greater concentrations in the CSF, intra-arterially into a limb, head and neck or the liver to achieve localized effects at these sites and intraperitoneally or intrapleurally to increase the local concentration of the drug (s).

Drug therapy of oral cancers: Carcinomas of the oral cavity present as non-healing ulcers, changes in the fitting of dentures, or as other painful lesions.

1. For small localized lesions in the oral cavity, surgery is preferred to avoid long term complications of radiations, such as xerostomia and dental decay.
2. For locally advanced disease, with metastasis in the lymph nodes – extensive surgery or radiotherapy,

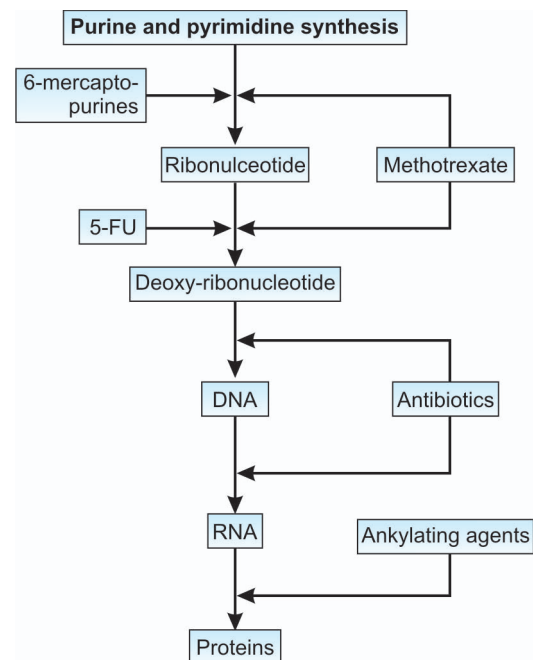


Fig. 13.1.2: Drug acting on protein synthesis

if surgery is not possible, is employed. Most cancers reoccur, usually within two years and cause death. To improve the survival period, cytotoxic drug therapy with cisplatin and 5-fluorouracil, with or without bleomycin or mitomycin, is given before surgery or radiotherapy.

Treatment of xerostomia- (dryness of mouth) following radiotherapy can be relieved by:

1. Frequent sips of cold drinks, sucking pieces of ice or sugar free fruit drops.
2. Use of artificial saliva of neutral pH and having electrolyte composition corresponding approximately to the normal saliva.
3. Pilocarpine nitrate tablets, 5 mg, orally, three times a day with or after meals.

ALKYLATING AGENTS

Actions: Alkylating agents exert cytotoxic, immunosuppressant and radiomimetic effects (similar to radiotherapy).

Mechanism of action: These drugs form highly reactive derivatives which transfer alkyl groups to various cellular constituents and bind them with covalent bonds. Alkylation's of DNA results in breakage of DNA strand.

Mechlorethamine: (Mustine HCL) is given IV as it is a highly irritant compound. It is used in Hodgkin's (MOPP regime) and other lymphomas.

Cyclophosphamide is converted to its active metabolite aldo-phosphamide in the body. It can be given orally. It causes cystitis due to a metabolite acrolein. This can be prevented by giving IV *Mesna*, irrigating the bladder with *acetylcysteine*, and by taking in large amounts of fluids. *Mesna* and *acetylcysteine* contain –SH groups which bind the toxic metabolites and inactivate them.

Cyclophosphamide is used in Hodgkin's lymphoma, leukemias in children and as an immunosuppressive agent.

Ifosfamide has actions and toxicities similar to cyclophosphamide.

Chlorambucil is very effective against lymphoid series. It is the drug of choice in chronic lymphocytic leukemia.

Melphalan is given orally in multiple myeloma.

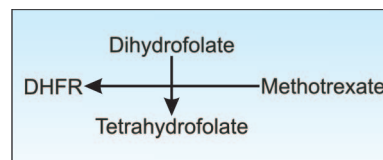
Busulfan (MYLERAN) has selective activity against cells of the myeloid series and is the drug of choice in chronic myeloid leukemia.

Nitrosoureas are effective in meningeal leukemias and brain tumors because they cross the blood-brain barrier.

Dacarbazine is useful in malignant melanoma.

ANTIMETABOLITES

Methotrexate: It is dihydrofolate reductase inhibitor: It binds to dihydrofolate reductase and prevents the formation of tetrahydrofolate (THF). This THF is a coenzyme essential in several reactions in protein synthesis. The deficiency results in inhibition of protein synthesis. Thus rapidly multiplying cells are most affected.



Actions

- Cytotoxic actions – methotrexate mainly affects bone marrow, skin and gastrointestinal mucosa.
- It also has immunosuppressant and anti-inflammatory properties.
- Methotrexate toxicity can be largely prevented by administering folinic acid. This folinic acid gets converted to a form of THF that can be utilised by the cells.

Uses of Methotrexate: It is curative in choriocarcinoma and is useful in acute leukemias, breast cancer and soft tissue sarcomas. It is also used in rheumatoid arthritis and psoriasis.

6-Mercaptopurine (6-MP): It is converted to a metabolite which inhibits purine synthesis. 6-MP is metabolised by xanthine oxidase. Allopurinol inhibits xanthine oxidase and thus prolongs the action of 6-MP.

Uses: 6-MP is used in acute leukemias in children, choriocarcinoma and some solid tumors.

5-Fluorouracil: (5 FU) inhibits the synthesis of thymidylate and thereby inhibits DNA synthesis. It is used in carcinoma of the stomach, colon, rectum, breast, and ovaries.

Cytarabin arabinoside: It is the drug of choice in acute myeloid leukaemia in adults. Also used in the treatment of Hodgkin's & Non-Hodgkin's Lymphomas.

ANTIBIOTICS

Actinomycin D (Dactinomycin) acts by inhibiting DNA-dependent RNA synthesis. It is one of the most potent anticancer drug and is used in Wilms tumor, rhabdomyosarcoma, choriocarcinoma and some soft tissue sarcomas.

Daunorubicin and doxorubicin

- They act by inhibiting DNA synthesis. Cardiotoxicity with hypotension, arrhythmias and CCF, is unique to both these drugs. They also cause vomiting, stomatitis, alopecia and bone marrow depression.

- Daunorubicin is used in acute leukemias while doxorubicin is useful in solid tumors and in acute leukemias. *Epirubicin and mitoxantrone* are analogs of doxorubicin which are less cardiotoxic.

Mitomycin C is converted to an alkylating agent in the body. It is used in cancers of the stomach, lungs and cervix.

Bleomycin

- It forms free radicals and causes breakage in DNA strand. It has the advantage of the unique mechanism of action and is less toxic to the bone marrow—this is advantageous in combination regimens.
- It is used in solid tumors—testicular tumors, squamous cell carcinoma of the head, neck and esophagus.
- It's most serious toxicity is pulmonary fibrosis and cutaneous toxicity but does not cause significant bone marrow depression.

Mithramycin (Plicamycin) is highly toxic, used in disseminated testicular tumors and in severe hypercalcaemia due to bone cancers. It reduces plasma calcium levels by its action on osteoclasts.

VINCA ALKALOIDS

Vincristine and vinblastine are obtained from vinca rosea, the periwinkle plant. They bind to microtubules in the mitotic apparatus and arrest cell division in metaphase. They are spindle poisons. The alkaloids differ in toxicity.

Vincristin (ONCOVIN). Vincristine is neurotoxic while bone marrow depression is less. It is used in leukemias, Hodgkin's lymphoma, Wilms' tumor and brain tumor.

Vinblastine causes bone marrow depression, alopecia and vomiting. It is used with bleomycin and cisplatin (VBC) in testicular tumors; it is also useful in Hodgkin's lymphoma.

HORMONES IN CANCER CHEMOTHERAPY

Glucocorticoids: Due to their lympholytic action, glucocorticoids are used in acute leukemias and lymphomas. Rapid clinical improvement is seen but duration can vary from 2 weeks to 9 months. They are used for initiation of therapy due to their rapid action.

Glucocorticoids are also of value in the following:

- With radiation therapy to reduce radiation edema
- In intracranial tumors to reduce cerebral edema and
- For symptomatic relief in critically ill patients.

Prednisolone or dexamethasone are commonly used.

Estrogens are useful in (i) **prostatic carcinoma** as it is an androgen dependent tumor, (ii) **breast cancer** in males

and in postmenopausal women—estrogens are used in advanced cases where surgery or radiotherapy cannot be employed.

Anti-estrogens: Tamoxifen is an estrogen receptor antagonist used in estrogen receptor containing breast cancer.

Progestins are useful in the palliative management of endometrial carcinoma.

Androgens are used in the palliative treatment of breast cancer in postmenopausal women along with oophorectomy.

Antiandrogen: Flutamide is used in prostatic cancer.

Fostestrol also used in carcinoma prostate.

MISCELLANEOUS

Procarbazine is effective orally in Hodgkin's lymphoma (MOPP regimen component). It damages DNA. This may make it carcinogenic.

Cisplatin gets converted to its active form in the cell, inhibits DNA synthesis and causes cytotoxicity. It causes ototoxicity, nephrotoxicity, peripheral neuropathy, nausea, vomiting and anemia. Anaphylactoid reactions can follow its use. It is relatively less toxic to bone marrow. Cisplatin is used in ovarian and testicular tumors and cancers of the head and neck.

L-asparaginase: The amino acid asparagine is synthesized by normal cells but malignant cells are unable to synthesize asparaginase and depend on the supply from the host. Asparaginase is an enzyme that converts asparagine to aspartic acid and deprives the malignant cells of asparagine supplies resulting in inhibition of protein synthesis. It is used in acute leukemias.

GENERAL ADVERSE EFFECTS TO ANTICANCER DRUGS (Table 13.1.1)

Since most anticancer drugs act on the rapidly multiplying cells, they are also toxic to the normal rapidly multiplying cells in the bone marrow, epithelial cells, lymphoid organs and gonads. Thus the common adverse effects are:

- **Bone marrow depression:** resulting in leukopenia, anemia, thrombocytopenia and in higher doses—aplastic anemia. In such patients, infections and bleeding are common.
- **Other proliferating cells:** GIT – stomatitis and ulcers; alopecia (loss of hair), reduced spermatogenesis in men and amenorrhea in women (due to damage to the germinal epithelium).

Table 13.1.1: Specific adverse effects of some anticancer drugs

Drug	Specific adverse effects	Other prominent adverse effects
Cyclophosphamide	Cystitis	Bone marrow depression, alopecia, stomatitis, vomiting, amenorrhea, teratogenicity
Busulfan	Pulmonary fibrosis	Bone marrow depression, alopecia, stomatitis, vomiting, amenorrhea, teratogenicity
Cisplatin	Ototoxicity	Renal dysfunction
Bleomycin	Pulmonary fibrosis, edema of hands	Stomatitis, alopecia
Daunorubicin	Cardiotoxicity, red colored urine	Bone marrow depression, alopecia
Doxorubicin	Cardiotoxicity	Bone marrow depression, alopecia
Mithramycin (Plicamycin)	Hepatotoxicity	Thrombocytopenia
Vincristine	Neurotoxicity, Peripheral neuritis	Muscle weakness, alopecia
Asparaginase	Pancreatitis, hepatotoxicity, mental depression	Allergic reactions
Mitotane	Dermatitis, mental depression	Diarrhea

- **Immediate adverse effects:** Nausea and vomiting are very common with most cytotoxic drugs. Prior treatment with powerful antiemetics is required.
- **Teratogenicity:** All cytotoxic drugs are teratogenic and are therefore contraindicated in pregnancy.
- **Carcinogenicity:** Cytotoxic drugs themselves may cause secondary cancers, e.g. leukemias are common after treatment of Hodgkin's lymphoma.
- Apart from the above, the adverse effects unique to some drugs are discussed under individual drugs.

Responses of tumors to cytotoxic drugs

1. Cancers for which chemotherapy can be curative:
 - Acute lymphoblastic leukemia ALL in children
 - Acute myeloid leukemia. (AML)
 - Choriocarcinoma
 - Non-Hodgkin lymphomas
 - Wilm's tumor.
2. Tumors that are sensitive to chemotherapy, resulting in remission that generally prolong life:
 - Breast carcinoma.
 - Chronic lymphocytic leukemia.
 - Ovarian carcinoma.
 - Osteogenic sarcoma.
3. Tumors that are sensitive to chemotherapy where life is sometimes prolonged:
 - Cervical carcinoma.

- Gastric carcinoma.
- Head and neck tumors.

4. Tumors that are refractory to currently available chemotherapy:
 - Colorectal carcinoma.
 - Non-small cell bronchogenic carcinoma.
 - Carcinoma of the pancreas.
 - Melanoma.

Drug Interaction

- With alcohol procarbazine produces disulfiram like reaction.
- Salicylates, phenothiazines and sulfonamide displaces methotrexate from plasma protein binding site and produces toxicity.
- Xanthine oxidase metabolizes 6 MP, therefore if xanthine oxidase inhibitor (Allopurinol) is used with 6 MP, its concentration rises to toxic level and reduction of dose is required (approximately 1/3 to 1/4 th level).

Other Uses of Anticancerous drugs

1. **As immunosuppressant:** Cyclophosphamide, azathioprine, etc.
2. **To treat psoriasis:** Methotrexate
3. **To treat viral infections:** Cytarabine

4. **As an adjuvant in AIDS:** Hydroxyurea
5. **As an abortifacient:** Methotrexate
6. **In management of sickle cell anemia:** Hydroxyureas

Important terminologies related with chemotherapy

- **Induction of chemotherapy:** Also called primary chemotherapy.
- **Secondary chemotherapy:** Second Line or additional therapy.
- **Adjuvant chemotherapy:** Chemotherapy of the induction with therapy by surgery radiation.
- **Neo-adjuvant chemotherapy:** Initial chemotherapy prior to surgery/radiation to reduce tumor mass.



S E C T I O N

14

Dental Pharmacology

Dental Pharmacology and Therapeutics

DEFINITION

Dental Drug: *It can be defined as a drug that is being prescribed or used by a dentist in his general practice.*

Usually in dental prescription locally acting drugs are used more often as compared to systemically acting drugs except in the situations where systemic administration of the drugs are essential for example in severe pain, infection and in minor or major surgical procedures where drugs like analgesics, antibiotics and sedatives are used systemically. It should be considered that even locally acting drugs are also not absolutely free from minor or major systemic side or adverse effects.

DENTIFRICES

Dentifrices are therapeuto-mechanical aids meant for cleaning the teeth with the help of a toothbrush. They are available as tooth powders and toothpastes. They are also employed for filling and polishing the teeth. The powder should be of a fineness which passes through a 60-mesh powder sieve. Though the prime function of a dentifrice is to assist the brush in cleaning the teeth, addition of few specific substance like fluoride and antiseptics can produce some additional benefits. The ingredients of dentifrices are:

1. Detergents: Detergents are cleansing agents which act by following mechanism:

- Lowering the surface tension such as hard soap, i.e. they are having emulsifying properties.
- Dissolving fatty substances and mucous plaques and loosening the debris adhering to the teeth.
- Foaming and scrubbing the teeth, act as lubricants.
- Liberate oxygen such as hydrogen peroxide.

Hard soap: It has multipurpose action. It includes sodium ricinoleates, spoonanimales, sodium alkyl sulphate a pale yellow powder is effective in both acidic and alkaline medium and in hard water.

Other detergents: Sodium bicarbonate (act by dissolving proteins), hydrogen peroxide and sodium perborate (act by liberating free oxygen and detaching the debris).

2. Abrasive agents: Dental abrasives are fine powdered substances which assist mechanically the scouring action of the toothbrush. They are basically the inorganic salts of low solubility, e.g. pumice (light porous stone of volcanic origin), calcium phosphate, calcium and magnesium carbonates, magnesium oxide, charcoal, silicates and kaolin.

Uses:

- Whitening (polishing) the teeth and silver amalgam fillings.
- In toothpastes and tooth powders for cleaning the teeth.

3. Antiseptics: They are used in very small amounts. This small amount of antiseptics may not be sufficient to exhibit adequate antiseptic action. Commonly used antiseptics in dentistry are thymol, menthol, benzoic acid, boric acid, eugenol, calcium and magnesium peroxide (2–5%) and cinnamon (up to 1%). Eugenol has the odor of clove and is also a local anesthetic used for dental filling while thymol is a powerful antiseptic, used in mouthwashes and gargles.

4. Coloring agents: These agents are used to make the preparation more attractive and acceptable for commercial purpose. Liquor rubri, liquid azorubri, tincture cocci (2%), and caramini are used to impart **red color** while methylene blue (0.001%) is used to impart **blue color**. Red color in acidic mouthwashes is employed with magenta (0.05%).

5. Sweetening agents: Commonly used sweetening agent is saccharine. It enhances the palatability. Though sucrose can also be used, it causes fermentation and is therefore not preferred while lactose is less likely to do so.

6. Other agents: Other agents-used in dentifrices include fluoride compounds (stannous fluoride) which is added for reducing the incidences of dental caries. Binding

agents like gum acacia and mucilage of tragacanth, can be used.

A good preparation of dentifrice should possess the following properties:

- It must be caustic, should be pleasant in taste.
- It must be non-decalcifying and non-over-abrasive
- Sufficient cleansing action
- It must not affect the action and synthesis of saliva, and should not damage the gums or the teeth.

OBTUNDENTS (Table 14.1.1)

Obtundents are agents which are used to diminish or eliminate the dentine sensitivity so as to make the excavation procedure painless. Obtundents can act by one of the following mechanisms:

1. Destruction of the nervous tissue: e.g. *Absolute alcohol*.
2. Precipitating surface proteins: e.g. *Astringents like zinc chloride and silver nitrate*.

Paralyzing the sensory nerve endings: e.g. phenol, camphor, menthol, thymol, clove oil, benzyl alcohol, etc.

Properties

- It should be free from pain.
- There should not be any staining over the dentine.

Its penetration should be sufficient so as to remove the dentine sensitivity.

Limitations: With the use of obtundents, irritants may stimulate the formation of secondary dentine (if applied for long period) and pulp may shrink. This group of drugs is now mostly replaced by local anesthetics like lignocaine or xylocaine which are used topically for painless excavation.

DESENSITIZING AGENTS

Dentine sensitivity is the most common problem affecting thousands of people all over the world which is characterized by pain that could be elicited by mechanical, chemical or thermal stimuli, i.e. the patient experiences pain while eating specially hot and cold food, sweet or sour food or even sometimes while brushing the teeth. This hypersensitivity is either due to removal of enamel or denudation (exposure) of the root surface. Loss of enamel may be due to mechanical injury or chemical erosion due to acidic food. The root surface gets exposed either due to wrong habit of tooth brushing or due to chronic periodontal diseases.

Characteristic features of Desensitizing Agents

- They should be non-irritant, non-toxic.
- They should be rapid acting, easy to use and have a long-lasting effect.

Table 14.1.1: Different types of obtundent

No.	Obtundent	Mechanism of action	Specific properties
1.	Alcohol	Act by precipitating the proteins in the dentinal tubules. Used as 70% solution.	Benzyl alcohol can also be used. Painless, stainless and non-toxic to pulp. It can be used alone or in combination with chloroform.
2.	Phenol	Protoplasmic poison, numbness is produced by irritation.	Rapid action, stains the infected dentine. It can be used alone or in combination with chloroform and clove oil.
3.	Clove oil	It paralyses the free nerve endings after a brief initial stimulation with several other obtundents.	Volatile oil, non irritants but it stains yellowish to the dentine. Used isolated or in admixed
4.	Zinc chloride	It acts primarily by precipitation of dentinal proteins and liberating acid.	It is applied in concentrated form. It initially causes a short but sharp pain followed by rapid desensitization. It is more suitable for shallow cervical cavities.
5.	Silver nitrate	Action is similar to zinc chloride but less painful.	Disadvantage is that it stains the dentine black. Contact with gum should be avoided.
6.	Paraformaldehyde	Acts by slow liberation of formaline	Action is slow, without any pain. No staining, no other adverse effect except that formaline may penetrate the pulp and cause inflammation.
7.	Camphor, thymol, menthol	Act by initial stimulation followed by paralyzing the sensory nerve ending of the dentine.	Phenol can replace menthol. The combination is used in the proportion of 1:2:1.
8.	Cresol	Action and mechanism is similar to Phenol	Penetrability is relatively more.

No such single agent is available at present. Hence multi-modal approach could be employed.

Different Desensitizing Agents Used in the Management of Dental Hypersensitivity

1. Physical methods : Restorations-Glass ionomer.
 2. Tubule sealants : 4-Methacryloxyethyl trimellitate, of the tubule
 3. Agents occluding dentinal tubules: Tresiolan, Potassium oxalate and nitrate, Calcium hydroxide, Sodium and Stannous Fluorides and Formaldehyde
 4. Agents precipitating proteins:
 - a. Astringents: Silver nitrate, Zinc chloride
 - b. Precipitating tubule proteins: Strontium chloride and Formaldehyde causing occlusion
1. **Physical methods:** Restorations to cover the dentinal tubules using glass ionomer and composites are found to be effective in patients with eroded gingiva. A combination of glass ionomer and composite resins is more beneficial when compared to either agent used alone. In patients with gingival loss, soft tissue grafts cover the exposed dentin to relieve the sensitivity.
 2. **Tubul sealants:** The newer agents including 4-methacryloxyethyl trimellitate have been tried as desensitizers.
 3. **Agents occluding dentinal tubules**
 - a. **Fluorides:** High doses of fluorides act by hardening the dentine surface and is claimed to be effective in 3-4 weeks. Fluoride iontophoresis (2% NaF) may be used to occlude the dentinal tubule. The procedure is very effective but is expensive and may require repetition.
 - **Sodium fluoride paste or gel:** It is applied to dried sensitive area and left for 3 minutes. This leads to an increase in secondary dentine formation, which blocks dentine tubules and reduces sensitivity.
 - **Stannous fluoride:** It acts by inactivating enzymes within the odontoblastic process and by inducing mineralization within the dentine tubules which reduces sensitivity.
 - b. **Tresiolan:** It is prepared by mixing two siloxane esters. When applied to dentine, it polymerizes in the presence of moisture to form an organosiloxane resinous skin. This plugs the orifices of the dentine tubules and forms a mechanical barrier against various stimuli.
 - c. **Strontium chloride:** They have very high affinity for calcified tissues and they act by enhancing the rate of calcification which obliterates dental tubules.

d. **Potassium nitrate:** It acts by occluding the dentinal tubules through crystallization. Used as a tooth-paste twice a day, potassium nitrate (5%) is a popular and effective desensitizing agent.

e. **Calcium hydroxide:** It supplies calcium ions which hasten remineralization of the exposed dentin. But it has to be applied by a dentist and may require repeated application.

4. Agents precipitating proteins

a. **Astringents- Silver nitrate and Zinc chloride:**

They act by precipitating proteins. They cause permanent staining of the teeth and appear to be toxic to the gingival tissue and pulp and therefore not preferred now a days.

b. **Formaldehyde and Strontium chloride:** They act by precipitating proteins within the tubules and occluding them. They have been used in the form of dentifrices in the past but currently they are also not used.

BLEACHING AGENTS

Bleaching agents are the chemical agents used to remove pigmentation of the teeth. They include:

- a. **Oxidising agents:** Like sodium peroxide (50% aqueous solution), pyrozone (25% H_2O_3) and perhydrol (30% H_2O_2 in water) are commonly used oxidizing bleaching agents. Sodium peroxide forms sodium hydroxide on losing oxygen, therefore use of fat solvent is not necessary.
- b. **Reducing agents:** Like saturated solution of sodium thiosulphate (hyposulphate), which is used to remove the superficial staining with silver (Ag), permanganate and iodine.
- c. **Chloride compounds:** A mixture of chlorinated lime and a few drops of acetic acid is used, this leads to liberation of chlorine. Sometimes, liquor sodium chlorinate may be used but potency is very less.
- d. **Ultraviolet rays:** It can be used for bleaching of the dentine from a carbon or mercury arc lamp or some modern device.
- e. **Iontophoresis:** Hydrogen peroxide can be used to remove stains from the teeth.

Specific Stain Treatment

1. **Silver stain:** bleaching agents—hypochlorite.
2. **Iodine stain:** bleaching agents—weak ammonia or sodium thiosulphate.
3. **Aniline dyes:** bleaching agents—chlorinated lime + acetic acid.

4. **Iron stain:** bleaching agents—hypochlorites and oxalic acid.

MUMMIFYING AGENTS

Mummifying agents are the substances used to harden and dry the tissues of the pulp and root canal. This hardening makes the tissues resistant to infection and can maintain aseptic condition. This treatment is essential when it is not possible to remove the pulp and the content of root canal completely. Astringents and antiseptics are used either separate or in combination as a paste for this purpose. Some mummifying agents are:

- a. **Iodoform:** It acts by liberation of iodine. It is made into a paste with eugenol, phenol, tannic acid, cinnamon oil and glycerol for use as an mummifying agent.
- b. **Liquid formaldehyde:** It is used with zinc-oxide and glycerine with local anesthetics like lignocain to harden the tissues. It should be diluted 3 to 4 times with water before use.
- c. **Paraform:** It acts by releasing of formaldehyde very slowly and is used in combination with zinc oxide and glycerine or other combination like zinc oxide, cresol and zinc sulphate.
- d. **Cresol, tannic acid and ammonia silver nitrate:** These are the other substances which can be used as mummifying agents.

ASTRINGENTS

Astringents are agents which act by precipitating proteins in superficial cells of the skin or mucous membrane and inhibit or diminish their excretions or exudations when applied. This leads to the formation of an insoluble layer of precipitated protein and hardening (act as a mummifying agents) of the surface which ultimately:

- Protect the membrane from irritants.
- Protect the membrane by resisting bacterial infection.
- Check minor hemorrhages and reduce bleeding.
- Delay absorption from the surface.

Classification: They are subdivided into two groups :

A. Vegetable astringent

Tannic acid, catechu, gall and kremeria. Tannic acid possesses acid radicle, which precipitate gelatine and protein and therefore it is an powerful astringent. It hardens superficial cells, reduces mucous secretions, prevent toxin absorption and prevent inflammatory reactions. Used in lotions (3 to 5%). Catechu has similar actions like tannic acid.

Uses:

1. As mummifying agent
2. As hemostatic agent
3. As obtundent
4. As astringent dentifrice
5. As an astringent mouthwash

B. Metallic Astringent

Salts of zine, copper, iron, aluminium and silver, lead; also alum.

Alum: It acts by precipitating proteins, it is an astringent, hemostatic agent, antiseptic. **Copper sulphate:** It is specifically used for the treatment of indolent ulcers of gums and to syringe pyorrheal pockets. **Zinc chloride:** It is a caustic astringent useful for aphthous ulcers, ulcerative gingivitis and for syringing pyorrheal pockets. Other astringents includes **Ferric chloride** solution and **Lead acetate**, but because they stain the teeth, therefore these are rarely used now a days, while **Silver nitrate** and **Mercuric chloride** are the weak astringents.

Uses:

1. As an astringent mouthwash for stomatitis.
2. As astringent paint for mastoiditis.
3. As hemostatic agent.
4. As lotion for chronic alveolar abscess.
5. As astringent for syringing pyorrheal pockets.
6. As astringents for ulcerative gingivitis and aphthous ulcer.

MOUTHWASHES

Mouthwash is meant to rinse the mouth with mechanical cleansing action and freshening action (deodorising the oral cavity). Approximately 15-30 ml of the diluted solution is used for rinsing and gargling the mouth for at-least 30 seconds to one minute. Mouthwashes contain astringents, antiseptics with or without obtundents, coloring and sweetening agents. They are also helpful in reducing plaque formation and in the treatment of various diseases discussed below. They are of various types which includes mouthwash for daily use, antiseptic and astringent mouthwash, detergent mouthwash, obtunding mouthwash and some specific mouthwashes. Prolonged use of concentrated solutions result in staining.

Types of Mouthwashes

1. **Mechanical cleansing mouthwash:** It contains (NaCl- 1.5%, NaHCO₃ – 1%, chloroform water 50 ml, and water up to 100 ml) must be diluted with equal volume

of warm water or compound thymol glycerine (glycerol 10%, thymol 0.05% with coloring and flavoring agents)

2. **Plaque inhibitory mouthwash:** Chlorhexidine–2% mouthwash or 1% gel, it specifically inhibits plaque formation on teeth.
3. **Antiseptic mouthwashes:** They contain cetylpyridinium chloride 0.05%, povidone iodine 1%. Other mouthwashes also contain oxidizing agents like hydrogen peroxide 6% or sodium perborate 68.6%, are useful for the treatment of acute ulcerative gingivitis (anaerobic-organism) + They also possess mechanical cleansing property.
4. **Obtundent mouthwash** for sensitive oral lesion: It contains (zinc chloride + resorcinol)
5. **Detergent mouthwash** used for cleansing and deodorising action.

For different specific problems of the oral cavity, different and specific mouthwashes are available, e.g. Amphotericin B or nystatin mouthwash for oral candidiasis, pilocarpine mouthwash for xerostomia, tannic acid mouthwash for the prevention of bleeding after oral surgery, etc.

Uses

1. Sensitive oral lesions
2. Halitosis (bad breath)
3. Soreness under dentures
4. Postoperative and other bedridden patients for maintaining oral hygiene; mouthwashes are also refreshing
5. Stomatitis
6. Surgical impaction-after removal of impacted tooth.

Chlorhexidine (CHLORHEX REXIDINE) and Povidine iodine (BETADINE) are some commonly used mouthwashes.

DRUGS USED IN DENTAL HEMORRHAGE

Postoperative hemorrhage is one of the most common complication of dental extraction. Prolonged bleeding following extraction of the tooth is usually the first indication of a hemostatic abnormality.

Dental hemorrhage is usually managed by careful suturing, debridement of socket and application of firm pressure, preferably under local anesthesia.

Local hemostatics are also called **styptics**. On its application they control (arrest) local bleeding following extraction of the tooth and other dental procedures. Some important styptics are:

Local Hemostatics (Styptics)

- Epinephrine (Adrenaline) in 1:1000 dilution. It controls bleeding by vasoconstriction
- Thrombin powder

- Thromboplastin powder
- Tannic acid (Astringent).

Some important styptics are discussed below:

Oxidized cellulose: It is treated with nitrogen dioxide and it stops bleeding by forming a clot on moistening.

Human fibrin foam: An alternative absorbable agent which can be packed into the socket and sutured if required.

Gelatin sponge: It is used to treat bleeding tooth socket and can remain in position for 2 weeks and later on absorbed completely.

Vasoconstrictor agents: They include adrenaline and nor adrenaline 1 : 10,000 solution of adrenaline soaked in sterile cotton is commonly used in tooth-sockets.

Aluminum chloride solution: Aluminium chloride solution of 5-10% has been used and these produce some hemostasis. Concentration stronger than this results in tissue destruction and are not recommended.

Ferric sulfate solution: NF (Monsel's Solution): This solution is a styptic form of astringent and is applied with cotton pellets. It is more effective if applied under pressure.

Side effect: Black stain on teeth.

Gingival retraction cords: Cords impregnated with local hemostatic agents such as epinephrine, aluminum chloride or ferric sulfate.

It should not be used in patients with cardiovascular diseases.

- Thrombin powder: It is dusted over bleeding surface.
- Thromboplastin powder: It is used as styptics specially in surgical procedures.
- Astringents: Tannic acid are used.

DISCLOSING AGENTS

Disclosing agents are the agents (dyes) which are used to make the supragingival plaques visible. Dental plaques are usually invisible. To stain the plaque, solutions of disclosing agents may be used either by painting the teeth with a cotton swab or by chewing the tablet and then rinsing the mouth with water.

Following are the examples of disclosing agents:

Fluorescein dye: Fluorescein dye stains the plaque yellow on application. It does not stain the soft tissues. It requires special UV light to see the stained plaque.

Erythrosin: Erythrosin dye stains the plaque area red but it may also stain the soft tissues. It is the most commonly used disclosing agent.

Two-tone dyes: It is a solution containing a combination of two dyes. New plaques are stained red, while mature plaques are stained blue, therefore it can be used to differentiate mature and immature plaque and it also do not stain the gingival tissues.

DENTAL PLAQUE AND ITS TREATMENT

Periodontal Diseases and Management

Classification of periodontal diseases:

1. **Inflammatory diseases:** Gingivitis, Periodontitis (Pyorrhea)
2. **Dystrophic diseases:** Gingivosis, Juvenile Periodontitis
3. **Neoplastic diseases**
4. **Anomalies**

Plaque is a thin transparent, soft biofilm deposits on tooth surface containing microorganisms which could be mineralized or non-mineralized. These deposits are formed on inadequately cleaned teeth. Poor oral hygiene and carbohydrate rich diet encourage plaque formation. Plaque contains 80% of water.

Plaque is the most important factor responsible for periodontal diseases as it induces inflammation of gingival and periodontal fibers. It is more harmful than calculus because it contains more bacteria and causes more irritation to gingival tissues. Therefore complete plaque removal by any means i.e. by mechanical or chemical means is therefore essential in controlling and preventing periodontal diseases.

Treatment: Plaques are more harmful and dangerous than calculus because it contain more micro-organisms specifically (*strept. mutans* and *strept. sobrinus*), causes irritation to gingival tissue and are more susceptible to periodontal disease and caries. Therefore all plaque should be removed as quickly as possible. Suitable antibacterial agents (antibiotics) are used to control these organisms (infection). Alternatively it can also be treated by altering tooth surface to prevent the bacterial attachment to the plaque.

Antibacterial Agents. *Penicillins, aureomycin, erythromycin and tetracyclines* are used systemically while *bacitracin, kanamycin, vancomycin and polymyxin-B* are used as topical mouth rinses or gels. Long-term use of antibiotics should be avoided because of the risk of toxicity. Preference should be given to those antibiotics which are not absorbed from the oral mucosa. Tetracyclines given systemically or as a mouth wash or by direct irrigation reduces bacterial colonization of teeth and periodontal pockets. **Systemic administration of metronidazole or**

tinidazole retard plaque formation and the development of gingivitis. Other agents that can be used in plaque control are:

Fluorides: Fluorides inhibit enzymatic reactions involved in glycolysis.

Oxygenating agents: Like hydrogen peroxide and sodium perborate. They act by liberating nascent oxygen.

Enzymes: They are the mucinases, extracts from dried pancreas containing trypsin, chymotrypsin, lipase, amylase, dextranase, etc. which are incorporated in chewing gums and toothpaste.

Halogens: They releases chlorophors and iodophors which act like (antiseptics) and are used in many mouthwashes.

Bis-biguanides: Chlorhexidine and Alexidine are also used as antiplaque agents. They are used as mouth rinses, gels and in dentifrices for the control of plaque and gingivitis.

Antiseptics: i.e. Chlorhexidine 0.2% aqueous solution as mouth wash is also quite effective.

DENTAL CARIES AND THEIR TREATMENT

Dental caries is a slowly progressive, degenerative, infective, irreversible condition characterized by demineralization and decay of hard and soft parts of the teeth resulting in cavitations and disintegration.

Role of carbohydrate and acids: Easily fermentable carbohydrate, e.g. sucrose plays an important role in the development of caries. Fermentation of carbohydrates in the oral cavity results in the production of acids like lactic acid, aspartic acid etc. These acids are responsible for demineralization and decalcification of the teeth. Carbohydrates also leads to synthesis of certain polysaccharides (**glucan, levan and dextran**) in the presence of certain enzymes, these polysaccharides hold the plaque tightly over tooth surface and therefore responsible for caries.

Role of microorganisms: Dental caries is a bacterial disease. Streptococcal mutans and lactobacilli are the important strains responsible for caries. These bacteria forms large amount of sticky, insoluble polysaccharides and also produces lactic acid from sucrose which is responsible for caries.

Role of plaque: Plaque is a thin transparent, mucinous film over tooth surface. This film may hold the bacteria over tooth surface. It also prevents the escape of acid into saliva and therefore indirectly responsible for dental caries.

Thus both organic and inorganic matter of the teeth are destroyed. As the process continues, the pulp is penetrated and the infection may spread into the systemic circulation.

Prophylaxis [Prevention of caries]: Dental caries can be prevented by the following measures:

- Public education especially to children regarding dental hygiene, proper use of toothbrush, dentifrices and prevention of caries (early management)
- Soluble carbohydrates should be avoided specially in the person who are suffering from dental caries. Sweets, ice-creams, chocolates, etc. are rich sources of soluble carbohydrate and are also good substrate for bacterial growth.
- “Fluoride therapy” can be used to increase resistance of the host.
- Prevent formation of plaque, by using anti-plaque drugs.
- Try to reduce ‘in-between’ eating habits.

Treatment

Fluorides: Fluoride, a halogen (electronegative compound) has been shown to reduce the incidence of dental caries. Its suggested mechanism of actions are:

- It inhibits the bacterial enzymes which are responsible for producing lactic acid and therefore prevents acid decalcification of the tooth structures.
- Hydroxyapatite is the major constituent of the enamel and dissolves easily in the presence of lactic acid. Application of sodium fluoride either internally or externally converts hydroxyapatite of enamel, dentine or bone to fluorapatite which is more resistance to acid attack. Thus fluorides make the outer layers of enamel harder and more resistant to demineralization.
- It inhibits plaque formation and also reduces anaerobic glycolysis and lactic acid formation within the formed plaque.

Systemic administration via water supply

- 0.5-l ppm i.e. 1 part of fluorine to 1 million part of water is considered adequate for prophylaxis purpose. Fluoridation of drinking water is the most effective measure in preventing dental caries, if consumed prior to eruption of the permanent teeth. Several large-scale studies have established the beneficial effects of optimum fluoridation of communal water supplies in preventing caries. More than 1-2 ppm results in toxicity, causes dental fluorosis.
- Adequate prophylaxis can also be achieved by supplementing fluorine in the form of sodium tablets (1 mg F/ tablet) in diet. It is suggested that using one tablet a day during the period of tooth development to nursing mother and to children up to the completion of calcification of third molars.

Topical application

- 2% sodium fluoride, or 8-10% stannous fluoride once a week for 4 weeks also prevent caries.

- Fluoride (dentifrices) mouth rinses [0.2% sodium fluoride solution containing 900 ppm of fluoride] for one minute-to be used twice a week will also effectively prevent caries.
- The topical application of sodium fluoride every six months may result up to 40% reduction in the incidence of dental caries.

Toxicity

Acute toxicity: It results from accidental or suicidal ingestion of fluoride-containing rat poisons. 2.5-5 gm is the lethal dose in adults. Symptoms due to overdose include nausea, vomiting, burning abdominal pain and diarrhea. Hypotension and cardiac arrhythmias are the cardiac manifestations.

Chronic toxicity: It results due to ingestion of fluorine over a long period or in a higher dose (more than 2 ppm / day regularly). Dental fluorosis leads to mottling of the enamel. Mottled enamel occurs as dull paper white patches over the surface of the enamel and brownish discoloration of teeth. Skeletal fluorosis resembles osteomalacia histologically characterized by joints pain and stiffness, osteosclerosis of the spine and pelvis causing spontaneous fractures.

Antibiotics: Dentifrices containing penicillin, chloramphenicol, bacitracin and streptomycin can be used to reduce bacterial index. But using antibiotics alone is not sufficient to prevent caries formation.

Silver nitrate: Area should be cleaned properly, careful assessment of infection should be done and then silver nitrate is applied on the deciduous teeth.

Chlorophyll: This green colored pigment found in leaves of the plants is found to be beneficial for dental health and protective against dental caries.

ROOT CANAL THERAPY AND APEXIFICATION DRUGS USED FOR FILLING ROOT CANAL

- First of all rendered aseptic cleaning of root canal is required before using the materials for the root canal.
- Root canal therapy and apexification is done on those teeth, where inflammation has extended in radicular pulp also.
- The material used for filling should be insoluble and non-irritant.
- In root canal procedure, all the pulpal tissues either radicular or coronal, are removed and root canals are prepared to retain an inert obturating material.
- The obturating material generally used should be able to seal the apex of the root, the dentinal foramina and

tubules. They should act as firm barrier against bacteria and moisture.

- Commonly used materials are gutta-percha, chlora-percha (10% gutta-percha in chloroform), euco-percha (10% gutta-percha in eucalyptol), silver amalgam, silver points.
- Combination of any two or more of the above may be used.
- Many pastes were used previously for the same purpose such as:
Oxpera containing equal parts of cresole, formaldehyde, and alcohol mixed with a powder composed of alum, thymol and zinc oxide each 25 parts.
- Apexification is the procedure in which apex formation is induced in the tooth by replacing necrosed pulpal tissues with calcium hydroxide paste or camphorated chlorophenol.
- Only a small amount of pulpal tissue is left which causes the apex formation.
- Apexification is done in immature permanent teeth with wide open apices (blunderbuss apices), because preparation and obturation of these teeth is too difficult.

DRUGS USED IN THE TREATMENT OF ORAL INFLAMMATION, ULCERATION AND ORAL PAIN (Table 14.1.2)

Oral mucosal inflammation/ulceration may be caused by trauma (physical or chemical), recurrent aphthae (small white spots on the mucous membrane of mouth seen in thrush), sprue or with vincent's angina, carcinoma, infections, nutritional deficiencies, gastrointestinal diseases, hemopoietic disorder and drug therapy. It is necessary to establish the diagnosis, so that the treatment can be directed to the cause. Local treatment is given to protect the ulcerated area, reduce inflammation and relieve pain.

Plain mouthwashes: A plain saline or thymol glycerine mouth wash is used to relieve pain in traumatic ulceration.

Local analgesics: Oral diseases and dental proceduring often results in postoperative pain which may be mild (expected after scaling), moderate (expected after simple extensive oral surgery).

Mild variety of pain can be treated with an analgesic like (aspirin or acetaminophen)

Drugs Used for the Treatment of Moderate Pain

Aspirin

Dosages: In adults 650-1000 mg, 4-6 hourly, orally.

In children 10-20 mg/ kg per day.

Preparations:

ECOSPRIN: Tab. 325 mg (Aspirin)

DISPRIN: Tab. aspirin 325 mg + Calcium carbonate 97.5 mg + Anhydrous citric acid 32.5 mg.

Contraindications: Gastric ulcer, bleeding disorders or anticoagulant therapy, asthma, gout, allergy, nasal polyp.

Side Effects: Nausea, vomiting, allergy, liver damage, respiratory problems, etc.

Codeine: This drug is indicated in toothache, muscular pain, neuralgia and headache.

Preparations and dosage: Codeine sulfate - Tab. 15 mg. Dose up to 60 mg can be safely used.

Side effects: Nausea, vomiting, allergy, overdosismalaise, constipation, drowsiness, etc.

Pentazocine: It is substituted for codeine for treating moderate to severe pain in a dose of 50 mg (equivalent to 60 mg codeine)

Table 14.1.2: Drugs used for the treatment of severe pain

Generic name	Proprietary name	Dosage form	Dose
Morphine Sulphate	MORPHINE	Injection Tablets 10	8, 15 mg. IV stat 30, 60, 100 mg
Meperidine	PETHIDINE	Injection	50-100 mg IM stat
	PETHIDINE	Tablet 50 mg	50-100 mg hourly
Buprenorphine	NORPHINE	Tablet (Sublingual)	0.2 mg stat 6 hourly
Tramadol Hydrochloride	TRAMAZAC	Cap. 50 mg Inj. 50 mg/ml in 2 ml ampule	50-200 mg 8-12 hourly

Preparations: Pentazocine- **FORTWIN** Tab. 25 mg
Inj. 30 mg/ml. SC or IV

Side effects: Nausea, vomiting, allergy (rash) irritability, hypertension, tachycardia, respiratory depression, etc.

Contraindications: Allergy to the drug, pregnancy, patients of respiratory, liver and kidney disease, children less than 12 years of age and patients with history of seizures and head injuries.

Warnings

- Chances of addiction (habit forming).
- It causes disorientation, confusion, visual disturbances and hallucinations therefore it also interferes with driving and operating machinery.

Clove oil, Menthol: It contains-tincture of pellitory, water and alcohol 10%.

Contraindications: Drug allergy, pregnancy, liver disease, respiratory disease and kidney disease, patients with acute abdomen (spasms of biliary and urinary tract), patients with history of seizures, head injuries, along with anti hypertensive agents.

Side effects: These include lightheadedness, nausea, vomiting, sedation, hallucinations, excitement, euphoria, dysphoria and tremors.

LOCAL ANESTHETICS (LA) DENTAL

- Discussed in detail in the chapter of LA.

Lidocaine

- It is an amide.
- Chemical name-diethyl-amino-2,6 acetoxylidide
- It is used with 1:100,000 epinephrine during dental procedures.

Adverse Reactions: Rash, irritation, sensitisation.

Contraindications: Severe liver disease and hypersensitivity.

Precautions: Pregnancy, denuded skin and sepsis.

Preparation: Lidocaine-XYLOCAINE – 30 ml.

Mepivacaine

- Chemical name-1-methyl-2-6 pipecoloxylidide hydrochloride
 - Use: Dental procedures for infiltration and nerve block. This LA is extremely useful in patients with cardiovascular disease. This drug produces acceptable depth and duration of local anesthesia without a vasoconstrictor effect.
- Side effects:** Rash, irritation, sensitization, convulsions, respiratory depression following seizure.

Contraindications. Hypersensitivity, liver disease, and cardiovascular diseases.

Preparation: Mepivacaine- CARBOCAINE – 300 ml.

Procaine

- It is an ester type agent.
- Chemical name - 2-diethylamino ethyl-4-aminobenzoate hydrochloride.
- Use. This drug is recommended in dental procedures for infiltration and never block anesthesia.

It is very useful in patients with liver disease as it is not metabolized by liver.

Precautions: Since [PABA] Para-Amino Benzoic Acid (a metabolite of procaine) inhibits action of sulfonamides, therefore it should be used with caution in patients on sulfonamide therapy.

Preparation: Procaine-**NOVOCAIN**- 30 ml.

ANTISEPTICS AND DISINFECTANTS

Antiseptics: They are the chemical or drug which, when applied over the living surfaces, inhibits the growth and multiplication of bacteria without killing them.

Disinfectants: They are the drug or chemical which are used on non living or inanimate objects to kill the bacteria. Usually they are used for sterilizing the instruments.

Phenol: It is used as mouthwash in a concentration of 3%.

Cresol: Compared to phenol, it is three times more potent (while toxicity remain same)

- Cresol, tricresol and para-amino chlorphenol are used as root canal antiseptics.
- It is also commonly used as a disinfectant solution.

Chloroxylenols: For the sterilization of dental instruments it is broadly used in a concentration of 5% solution. example is Dettol.

Preparations: **DETTOL** - Chloroxylenol 4.8%, Absolute Alcohol 13.1% and Tersenol 9%.

Halogens

- **Chlorine:** It is a germicide and in dentistry it is used as sodium hypochlorite for irrigation of root canals (1% solution).
- **Iodine:** It is a strong bactericidal and fungicidal agent with little antiviral activity also. It is used as a sterilizing agent for skin prior to surgery in concentration of 2.5% iodine and 2.5% potassium iodide in an alcoholic solution. In traumatic periodontitis its weak solution is used as a counterirritant.

- **Povidone-iodine:** It is also used as a pre-surgical scrub. Preparations. Povidone-Iodine BETADINE- 1% W/V of available iodine and Absolute alcohol-8.38%.

Hexachlorophene: It is a bisphenol which is bacteriostatic in action (i.e. it inhibits the growth of bacteria rather than killing them).

- It is more effective against gram +ve than gram –ve organisms (bacteria)
- It is used as a scrub prior to any surgical procedure.

Chlorhexidine

- It is effective against both gram +ve and gram –ve organisms (bacteria)
- It is used for:
 - Wound cleaning (1:2000 solution)
 - Disinfecting instruments (3 minute immersion) and storage of instruments (0.5% solution in 70% alcohol)
 - Preoperative skin scrub (0.5% solution in 70% alcohol)
 - As a disinfectant in (root canal treatment) RCT (in a concentration 1.5% with cetrimide 15% solution)
 - As a daily rinse (0.2% solution) to inhibit deposition of bacterial plaque on tooth surface and at dento-gingival junction

Preparation

- Chlorhexidine-**PERIDEX**- oral rinse as 0.12% in 450 ml. bottle.
- Chlorhexidine- **HIBITANE**- 0.5% solution in alcohol-70%

Adverse effects: Altered taste sensation, staining of teeth and tongue.

Oxidizing agents: These act by releasing oxygen and water on coming in contact with body tissues.

- **Hydrogen peroxide:** It is useful as an antiseptic mouthwash (15-20 ml in a ½ tumbler of water) due to its antibacterial action. Ten volume hydrogen peroxide diluted with an equal quantity of warm water used for debridement of root canals in RCT.
- **Sodium perborate** as a mouthwash: It releases oxygen when comes in contact with body tissues and is used in management of acute ulcerative gingivitis but not in the chronic variety.

Quaternary ammonium compounds

They are derivatives of ammonium chloride and effective against both gram +ve and gram –ve organisms. They are used for the application to skin and mucous membranes and sometimes for sterilizing surgical instruments.

- Binzalkonium Chloride (ROCCAL, TEPHIRAN) and Cetrimide (CETAVLON) most commonly used.

- Cetrimide in combination with chlorhexidine is a popular dental antiseptic – CETRIHEX.

Alcohols: Ethyl alcohol (Ethanol) in a concentration of 50-70% by weight used as a skin antiseptic prior to injection.

Gum paints: They are mainly used as an antiseptic and gum astringent and are for topical use only.

Preparations

Tannic acid	30%
Glycerine	70%
Iodine	0.3%
Potassium Iodide	0.5%
Thymol	0.05%
Menthol	0.08%
Glycerine	qs

Mechanical barrier: Mechanical protection can be provided by applying carmellose gelatine paste.

Corticosteroids (topical)

- Corticosteroids like hydrocortisone acetate lozenges or triamcnenolone acetonide 0.1% topically or triamcnenolone hexacetonide intra-lesionally or betamethasone valearate topical spray is used for treating oral ulceration and mucosal lesions. Prednisolone is preferred for systemic use only.
- For treatment of pulpal inflammation, steroids are applied over exposed dental pulp. LEDERMIX – which is a combination of triamcnenolone + tetracycline is preferred.
- Intra-articular injection of hydrocortisone or prednisolone can be administered to control pain and inflammation of temporomandibular joint.
- Methyl – Prednisolone and betamethasone IM should be administered just prior to surgery for extraction of impacted third molar and after orthodontic surgery to reduce pain and inflammation
- Systemic steroid (prednisolone) should be prescribed to treat unilateral facial palsy (Bell's palsy).
- For treating anaphylactic shock, hydrocortisone IV along with adrenaline 0.2 ml in 1:1000 solution SC or IV and anti-histaminics should be given.

ADVERSE EFFECT OF DRUGS IN THE ORAL CAVITY

Xerostomia (Dry Mouth)

[Anticholinergic drugs]: Atropine, atropine substitutes and derivatives. Propantheline, oxyphenonium, benztrapine,

benzhexole, TCA [tricyclic antidepressant], phenothiazines, clonidine, etc.

Taste Disturbances [Partial or Total Loss of Taste]

Penicillamine, clofibrate, carbimazole, lithium carbonate, lincomycin, griseofulvin metallic taste: metronidazole, tinidazole, metformin, all heavy metals, etc.

Discoloration of

Mucosal tissue: Lead, chloroquine, phenothiazines, OCP, chlorhexidine.

Teeth: Tetracycline, chlorhexidine, iron salts, stannous chloride, etc.

Halitosis (Bad Breath)

Isosorbide dinitrate (sublingually), disulfiram.

Pain and Swelling of Salivary Glands

Oxyphenbutazone, iodides, bethanidine, methyldopa, clonidine, nitrofurantoin, chlorhexidine.

Gingival Hyperplasia and Hypertrophy

Phenytoin, oral contraceptives, nifedipine, cyclosporine.

Oral Ulceration

NSAIDs like Aspirin, potassium, isoprenaline (sublingually), naproxane, methotrexate, fluorouracil, actinomycin D, doxorubin, bleomycin.

Oral Infections Induced or Aggravated by Drugs

Corticosteroids, broad spectrum antibiotics (tetracycline and chloramphenicol), topical fluorouracil, immunosuppressive drugs, azathioprim, etc.

Treatment of Xerostomia (Dry mouth)

Dry mouth may be caused by damage or disease of the salivary glands or by the administration of drugs with antimuscarinic side effects – anticholinergic, antispasmodics, tricyclic antidepressants, antipsychotics, clonidine, or by irradiation of the head and neck.

Dry mouth can be relieved by:

1. Frequent sips of cold drinks, sucking pieces of ice or sugar free fruit drops.
2. Artificial saliva of natural pH and containing electrolytes corresponding approximately to the composition of saliva.
3. Pilocarpine nitrate tablets 5 mg orally, three times a day with or after meal. They are particularly useful in xerostomia following irradiation of head and neck cancer.



S E C T I O N

15

Miscellaneous Drugs

Chelating Agents

DEFINITION

These are the chemical agents or drugs with two or more than two electronegative group that can form stable covalent coordinate bonds with cationic metal atoms, i.e. they are the drug which provide “ligand” to the metallic ion and form a complex (ring) which is stable, non toxic and easily excretable. By this they interfere with normal cell functions which require these ligands. Heavy metals cannot be metabolized in the body.

Chelating agents or heavy metal antagonists bind the heavy metal ions and therefore make them non-toxic. The chemical complex formed is called chelate (chele=claw; in Greek). The process of complex formation is chelation. The complex so formed is water-soluble and is eliminated by the kidneys.

Some important chelating agents are:

- BAL (Dimercaprol): British antilewisite.
- Succimer (Dimercaptosuccinate)
- EDTA (Disodium edetate): Ethylene Diamino Tetra Acetic acid
- Diethylene Triamine Penta Acetic Acid, DTPA (Ca-disodium DTPA)
- Desferrioxamine
- Penicillamine deferprone.

Dimercaprol (BAL): British antilewisite: It is colorless oily liquid, given parenterally and developed by the British during World War II as an antidote to lewisite-an arsenical war gas. Hence it is also known as British Antilewisite or BAL. Required in 2 BAL: 1 metal ratio.

Indications

- a. Poisoning of As (Arsenic), Hg (Mercury), Au (Gold), Bi (Bismuth), Sb (Antimony), etc.
- b. As an adjuvant to penicillamine in copper poisoning.
- c. As an adjuvant to calcium disodium EDTA in lead poisoning.

Dose: 5 mg/kg stat followed by 2-3 mg/kg intramuscular every 4 to 8 hourly for 2 days (urine should be alkaline).

Adverse effect

- GIT disturbance like nausea, vomiting, etc
- Hypertension, tachycardia, headache and lachrymation, etc. (managed with antihistaminics).

Dimercaprol succimer (DMSA) and Dimercaprol sulfonate (DMSP): Their advantages over BAL are:

- More polar and therefore confined to extracellular space
- Less cellular toxicity
- Administered orally (effective)
- They are used specifically in the treatment of lead poisoning, specially in children; in arsenic and mercury poisoning, for prevention of renal stone formation in the patients with homozygous cystinuria.

Calcium disodium edetate (CaNa₂ EDTA): It chelates many divalent and trivalent metals like zinc, manganese, iron and lead. It is used in the treatment of lead poisoning. Given parenterally, lead deposits in the bone are mobilised, chelated and excreted through kidneys.

Indications: CaNa₂ EDTA is mainly used in the treatment of lead poisoning. It can also be used in zinc, manganese and iron poisoning. Sodium Edetate is used in severe hypercalcemia.

Dose: 1 gm diluted in 200-300 ml of normal saline infused over 1 hours

Adverse effects include:

- Fatigue, fever, myalgia but no tetany
- Nephrotoxicity and dermatitis.

d-Penicillamine: It is a dextro isomer and is prepared by degradation of penicillin but has no antibacterial activity. It chelates copper, mercury, zinc, and lead. It is orally effective.

Uses

1. Treatment of copper, mercury, zinc and lead poisoning.
2. Wilson's disease (hepatolenticular degeneration)-copper is deposited in liver and brain causing degeneration.
3. Treatment of severe rheumatoid arthritis.
4. Treatment of scleroderma
5. Cystinuria- promotes excretion of cysteine by forming soluble complexes and prevents formation of cysteine stones.

Doses: 0.5-1 gm/day orally.

Toxicity

- Patients allergic to penicillin may develop anaphylaxis; dermatitis may occur in some.
- On long-term use renal, hematological, dermatological and other toxicities can occur.
- Cutaneous: itching, burning sensation, etc.

Desferrioxamine: It is obtained from (actinomycetes) streptomyces. It has a high affinity for iron, forms stable complexes and removes iron from hemosiderin and

ferritin. It does not chelate the iron in hemoglobin and cytochromes. It is given parenterally. It has no affinity for heme iron (Hb).

Side effect: Allergic reaction range from rashes to anaphylaxis (rare), diarrhea, muscle cramps and blurred vision.

Uses

1. Acute iron poisoning-desferrioxamine is the drug of choice.
2. Chronic iron poisoning-as in thalassemia patients who receive repeated blood transfusion.
3. **Dose:** 0.5 to 1 gm/day intramuscular.

Side effect: Abdominal pain, loose motion and some time ophthalmic side effects.

Deferiprone

- It is an orally active iron chelator
- **Indication:** Acute iron poisoning
- **Side effect:** Agranulocytosis

Antiseptics and Disinfectants

Sterilization: It is a process, used to kill all the microorganisms, in both vegetative form and sporing states from any surface, article or a medium.

Disinfectant: They are the agents used for the destruction of *all pathogenic organisms but not spores*. A disinfectant is used on **inanimate** (i.e. instruments) objects only. They may be bactericide, viricide or fungicide.

Antiseptic: They are the agents (chemical) that destroys pathogens (microorganisms) and can be used on **animate** (i.e. living) tissues. The term germicide can be used for either drugs, i.e. (disinfectants and antiseptics). Germicides are widely used in domestic products like soaps, after-shave lotions and various cosmetic creams.

Deodorant: It is a substance which suppresses or neutralizes bad odours e.g. lime and bleaching powder.

CLASSIFICATION

Physical agents

1. Heat: Sunlight
2. Ultraviolet light

Chemical agents

1. Acids: Boric acid, Acetic acid, Mandelic acid, Benzoic acid.
2. Alkalis: Sodium and Potassium hydroxide.
3. Alcohols: Ethanol, Isopropyl alcohol.
4. Aldehydes: Formaldehyde, Glutaraldehyde.
5. Surfactants:
 - Anionic soaps: Sodium laural sulphate
 - Cationic soaps: Cetrimide, Benzalkonium, Benzethonium chloride.
 - Non-ionic soaps: Polysorbate
 - Phenol and related compounds: Cresol, Phenol, Resorcinol, Chlorhexidine, Chloroxylenol, Hexachlorophene, etc.

- Halogens: Iodine, Iodophores, Chlorine, Chloramines.
- Oxidizing agents: Hydrogen peroxide and other peroxides, Potassium permanganate, and zinc permanganate.
- Dyes: Acriflavin, Proflavine, Gentian violet, Methylene blue, etc.
- Antibiotics: Bacitracin, neomycin, polymyxin B.
- Heavy metals: Silver nitrate, Mercurial compounds, Zinc salts.
- Gases: Ethylene oxide.

Mechanism of Action of Antiseptics and Disinfectants

- Coagulation (denaturation) of bacterial proteins leading to destruction of microorganisms.
- Oxidation of bacterial protoplasm.
- Binding of SH groups essential for enzyme action (poisoning of enzyme system)
- Detergents (soap) like action.
- By affecting important properties of bacterial cell wall

Characteristic properties of an ideal antimicrobial agent

- It should be chemically stable,
- It should have a wide antibacterial spectrum,
- It should have rapid action and non-irritating to the tissues.
- It should not interfere with wound healing activity even in presence of pus, exudates and tissue degradation products.
- It should not be absorbed into systemic circulation.

Factors that Determine Therapeutic Efficacy of These Compounds

- Drug concentration and duration of contact except alcohol.

- Specific susceptibility of the organism, e.g. spores and viruses are resistant to many antiseptics.
- Temperature: A rise in temperature will increase antiseptic activity.

Heat: Moist heat, i.e. saturated steam (120°C) at approx. 2 atmospheric pressure is the most strongest agent for destroying microbes. It is effective against both vegetative and spore forms of most bacteria after an exposure for 15 to 20 minutes. Dry heat is comparatively less effective.

Ultraviolet light: A wavelength of approx. 2500 to 2700 Å has found to be most effective antibacterial effect. Gram negative bacteria are most sensitive, while staphylococci, streptococci and viruses are mostly resistant. It prevents airborne cross infections in burn therapy therefore it is used over there.

Acids

Boric acid and sodium borate (borax): It has weak bacteriostatic and fungistatic activity. It is also present in prickly heat powders and ear drops. Aqueous solutions of boric acid are used for irrigating eyes, bladder, vagina and large wounds.

Acetic acid: It is an antibacterial (at acidic pH) relatively weak antiseptic and antifungal agent. It is bactericidal above 5% and specially sensitive to pseudomonas. It is used for dressing in burn wounds.

Benzoic acid: It is basically bacteriostatic and used as a preservatives in food and drinks (0.1%). It has also possesses antifungal action therefore used in Whitfield's ointment (salicylic acid – 3%, benzoic acid – 6%) in the treatment of ringworm infection.

Alcohols

Ethyl alcohol: It is effective antiseptic at 40-90% concentration. It acts by precipitating bacterial proteins. The antiseptic activity decreases above 90%. 70% alcohol if rubbed on skin kills 90% of bacteria in 2 minutes, used before hypodermic injections. It is ineffective against spores and viruses.

Disadvantages

1. It is a poor disinfectant for instruments. It has poor activity against spores, some viruses and fungi and it also promotes rusting.
2. It should not be applied on mucous membrane and on open wounds. Irritant-causes burning when applied
3. Alcohols are flammable-should be allowed to evaporate before using cautery or laser surgery.

Uses: Ethyl alcohol is used to clean the skin before injections and in any surgeries. It is also used for the treatment of pain of trigeminal neuralgia.

Isopropyl alcohol: It is more toxic and has same potency as ethanol. It is used in 30 to 90% concentration as skin antiseptic.

Aldehydes

Formaldehyde: It is a pungent odor gas at room temperature and sometime used for fumigation. It has a broad anti-microbial spectrum. In a concentration of 1:200, it kills both spore forming and non spore forming organisms. Its 37% aqueous solution is **formalin** which precipitates protein and hardens skin and other tissues, therefore it is used for **preserving pathological specimens** and **embalming and preservation of cadavers**.

Mechanism of action: Aldehydes act by alkylation of chemical groups in proteins and nucleic acids.

Uses

- Used as a disinfectant.
- In the strength of 1:500, used as a mouthwash or gargle for hardening the gums.
- As an anhydrotic agent when applied to palm and soles.
- It is also used for disinfections of instruments and gloves. **Fiberoptic** endoscopes, respiratory therapy equipment, hemodialysers and dental hand pieces which cannot withstand high temperatures of steam sterilization.

Glutaraldehyde: It is a potent dialdehyde having high sporicidal and tuberculocidal activity. Used as a 2% solution buffered with sodium carbonate so that pH should fluctuate between 7.4 and 8.5. It is bactericidal, sporicidal, fungicidal and viricidal. It is less irritant than formaldehyde; does not damage lenses and cementing material in endoscopes. It loses its activity within 2 weeks of its preparation.

Uses

- It is used to sterilize surgical and endoscopic instruments, and plastic and rubber apparatus.
- Like formaldehyde, it has **anhydrotic** action when applied to soles and palms.

Surfactants or Surface active agents: They are also called as detergents or wetting agents. They are the chemicals that lower the surface tension of solution and therefore termed detergents. Structurally they contain both; one

hydrophobic group having affinity for fatty compound and one or more hydrophilic group. Soaps are anionic, and organic quaternary ammonium compounds or cationic surface active agents.

Anionic surfactants, e.g. soaps:

- They ionize (dissociate) in aqueous solutions to form hydrophobic moiety in the anion [a large and complex anion] which lowers the surface tension.
- They are effective against gram-positive and acid fast organisms only.
- Mode of action: They act by emulsification of the lipoidal secretions of the skin, in which bacteria resides. Microorganisms are enmeshed in the lather and washed away on rinsing they have a cleansing action.
- Anionic surfactants have a narrow spectrum of activity; but their germicidal activity can be increased by adding another antiseptic like hexachlorophene.

Preparation

1. Potassium hydroxide or sodium hydroxide + vegetable oil.
2. Sodium lauryl sulphate- It is effective in hard water.

Cationic surfactants: e.g. benzalkonium chloride, Cetrimide, etc.:

- They ionize (dissociate) in aqueous solutions to form hydrophobic moiety in the cation [a large and complex cation] which lowers the surface tension.
- They are more effective against gram-positive and gram-negative organisms (less active against spores, viruses and fungi)
- They are active in neutral solution.
- They are non-irritating and safe.
- Solutions up to 0.1% are used as **mouthwash** or on denuded skin as an antiseptic.
- **Dequalinium chloride is used in gum paints and lozenges.**
- **Cetylpyridinium chloride is used in mouthwashes and lozenges.**
- In a dilutions of 1:5,000 to 1:20,000 their antimicrobial activity covers a wider range of organisms, i.e.
 - 1:1000 solution for cleansing skin
 - 1:2000 for mucous membranes and denuded skin
 - 1:20,000 for irrigation of the bladder and urethra
 - It is also used for (1:1000-4000) storing sterilized surgical instruments.

Cetrimide (cetavlon): It is a cationic detergent with bactericidal activity when used as 1% solution. In higher dilution it is bacteriostatic. It is also used as a cream. Its 0.5 to 1% solution is very effective in disinfecting and cleansing wounds. SAVLON, which is a combination of [cetrimide 3% + chlorhexidine] is the most popular antiseptic.

Phenol Derivatives: It is one of the oldest antiseptics introduced by **Lord Lister** in 1860s, and marked the beginning of modern antiseptic techniques. No. of phenolic derivatives have been prepared and used as antimicrobial (antiseptic) agents.

Phenol (carbolic acid): Phenol is bactericidal and to a extent fungicidal also. It is quite effective against non-sporing pathogens but has poor action against spores and viruses. The antibacterial property of phenol is possibly due to presence of the phenolic – OH group which, acts by denaturing the bacterial proteins. It destroys cell membrane and is a protoplasmic poison. Phenol rapidly penetrates even intact skin and mucous membrane. It also possesses mild local anesthetic action.

Phenol is extremely irritant to exposed tissues (corrosive)- when swallowed, it burns buccal, esophageal and gastric mucous membrane.

Uses

- It is used as a local antiseptic and disinfectant against gram-positive and gram-negative bacteria's, fungi and some viruses.
- Phenol is used to disinfect urine, feces and sputum of patients.
- Sometimes it is used as an anti-pruritic agent because of its local anesthetic action.
- Even today phenol 5% + Almond oil is injected around internal hemorrhoids (**piles**) as a **sclerosing agent**.

Dettol: It is a liquid antimicrobial agent containing about 4.8% of **Chloroxylenol** (chlorinated phenol). It is effective against gram-positive and gram-negative organisms. Antiseptic cream contains 1 to 3% of chloroxylenol, 6.25% for cleansing wound and 5% solution in 70% alcohol is used for disinfections of surgical instruments.

Cresol: It is methyl-phenol, which is obtained by distillation of coal tar and consists of a mixture of ortho-, meta- and para-cresol. It is about 10 times more potent as compared to phenol, with same range of toxicity. It is used as a **commercial disinfectant**.

Lysol: Generally the cresol is not too soluble in water. Therefore cresol is emulsified in soap solution which is called **Lysol**: It has higher antiseptic activity and is a useful disinfectant for hospital and domestic use.

Resorcinol: It is an agent which is less potent antiseptic as compared to phenol, but are having extra features like **Keratolytic** and **antipruritic** activity. Prolong use leads to thyroid enlargement (goitrogenic). Systemic absorption may lead to CNS excitation.

Uses: In the treatment of skin infections like prurities, eczema, ringworm and psoriasis.

Hexachlorophene: It is a chlorinated phenol, which is mainly effective against gram-positive organisms and has weak action against gram-negative organisms. Hexachlorophene acts by inhibiting bacterial enzymes and causing lyses in a concentration of 2-5%. It is odorless and non-irritating substance and therefore can be easily applied on skin. It is used in soaps for surgical scrubbing and it effectively lowers the incidences of staphylococcal skin infections.

Uses

- For cleaning the skin in obstetrics,
- In the treatment of carbuncles, furuncles, acne, impetigo, fungal infections of nails and skin and seborrhoeic dermatitis.
- It also reduces body odor by preventing bacterial decomposition of organic material and therefore is used as a **deodorant**.
- In USA, hexachlorophene was used to wash newborn babies which resulted in brain damage in such babies and therefore use of > 3% hexachlorophene is banned over there.

Thymol: It has weak fungicidal and anthelmintic action. A mixture of iodides of thymol has been employed as dusting powder.

Halogens

Iodine: It is one of the oldest antiseptics. It has a broad spectrum of activity, is a powerful bactericidal, sporicidal, fungicidal and viricidal agent. A 1:20,000 solution kills most of the bacteria within 1 minute. The activity is inhibited by organic material but enhanced by alcohol.

Disadvantages

- It is irritating and painful (dermatotoxic), stains the area, and may delay wound healing. Rashes, fever and generalized skin eruption may develop in some patients who are sensitive to iodine. Prolonged systemic use causes **iodism** (i.e. hypersensitivity reactions)
- Oral ingestion of iodine in therapeutic dose may produces: nasal catarrh, conjunctivitis, lacrymation, bronchitis, and skin rashes.
- If taken during pregnancy, may causes goiter and mental retardation in the offspring.

Uses of iodine

1. Tincture iodine (I_2 in KI + alcohol): A 2.5% solution of elemental iodine with 2.5% potassium Iodide in water and 45 to 50% ethyl alcohol, used to clean skin before surgery. Iodine crystals are used to sterilize water for soaking vegetables and cleaning before use.

2. Mandl's paint: (compound Iodide paint): It consists of mixture of 1.25% Iodine, 2.5% potassium Iodide, in alcohol and glycerin. is used in the treatment of tonsillitis and pharyngitis.

3. Lugols solution: It is a strong iodine solution contains about 5% Iodine, and 20% potassium iodide. It is used in the treatment of iodine deficiency, thyroid disease and thyrotoxicosis.

4. Iodine ointment (solution): It is a 2.5% solution of elemental iodine with 2.5% potassium Iodide in water and used as strong fungicidal agent and also posses weak antibacterial action.

Iodophors: Iodophors are the soluble complexes (large organic molecule) of iodine with surfactants like (**detergents**). The detergents serve as carriers (carrying loosely bound iodine) and slowly release them, i.e. iodine. They are prepared by the interaction of iodine and polyvinylpyrrolidone, e.g. **Povidone iodine (BETADINE)**-5% solution.

Advantages: Iodophors are water-soluble, non-irritating and non-staining, less toxic and non-sensitizing to the skin.

Uses: Used for preoperative scrubbing, as local antiseptic in boils, burns, skin preparation, furunculosis disinfections of instrument, ulcers, ringworm and in oral/vaginal fungal infection.

Chlorine: It is a potent antimicrobial agent. It kills both gram-positive and gram-negative organisms in a very low concentration (0.1 PPM in 30 seconds). It also destroys some viruses, fungi and many protozoa in higher concentration. The anti-microbial activity of chlorine is reduced in presence of organic matter (algae and water weeds) since they bind chlorine and therefore need higher concentration of free chlorine.

1. Chloramines (organic chloride) are compounds that release chlorine slowly. The freshly prepared solution is used for **mouthwash**, irrigating bladder and urethra.
2. **Chlorinated lime** (bleaching powder) is obtained by the action of chlorine on lime. It contain about (30% w/w, of available chlorine). It is used as a disinfectant and deodorant.
3. On reacting with water, chlorine form **Hypochlorous acid** on the basis of which, chlorine is used in the disinfection of water and swimming pools.
4. Eusol is a solution of chlorinated lime with boric acid (**calcium hypochlorite solution**).
5. **Dakin's solution** is surgical chlorinated soda solution.
6. Other slow chlorine releasing substances are: Halazone, Chloroazodin, strong sodium hypochlorite solution, etc.
7. Its most important use in RCT (Root Canal Treatment in dentistry).

Oxidizing Agents

Potassium permanganate: It is an oxidizing agent and an astringent and oxidizes toxins and bacteria to make them inert. Its purple color crystals are water soluble and dissolved in 16 parts of water for use. It acts by liberating oxygen which oxidizes bacterial protoplasm. *Organic matter reduces its activity and the solution gets decolorized. It promotes rusting; concentrated solution is caustic and causes burns and blistering.*

Uses

- It is used as a deodorant and disinfectants.
- To purify well water.
- Solution of 1:4000-1:10000 potassium permanganate is used for **gargling, or mouthwash in stomatitis, to wash infected ulcers** and to irrigating cavities, urethra, bladder and wounds.
- For stomach wash in alkaloidal poisoning like opium and strychnine (except atropine and cocaine as these are not efficiently oxidized).
- 1% solution in mycotic infections like athlete's foot.
- 1:100-1:500 solution is used to disinfect bed pans and septic discharges.
- Used topically to oxidize snake and scorpion venom in case of bite.
- To disinfect vegetables fruits.

Hydrogen peroxide: It is a colorless and odorless liquid. As 3% solution, H_2O_2 has been extensively used for cleaning wound (weaker antiseptic) and as an deodorant. It has poor penetrability and $T_{1/2}$ (duration of action) is short. It liberates nascent oxygen when applied to tissues and then oxidizes bacteria and necrotic tissue. On keeping for long time, it loses its potency. On application, there is effervescence and this helps in removing tissue debris, ear wax, etc.

Uses

- Hydrogen peroxide is used for cleansing wound, abscesses and for irrigation.
- In **dentistry**, it is used to clean septic sockets and root canals and also as a **mouthwash and deodorant gargle**.
- It is used as ear drops while removing ear wax.

Sodium perborate: This agent resembles like hydrogen peroxide, produces its antimicrobial action by liberating oxygen, and having similar uses.

Dyes: Basically they are of two types: Acridine dyes and triphenylmethane dyes:

Acridine Dyes. [Acriflavine hydrochloride and proflavine hemisulphate]:

These acridine dyes are yellow in color and are active against gram-positive bacteria and gonococci (proflavine is better).

They are **bacteriostatic**, non-irritant and gram-negative bacteria are much less sensitive. Their potency and efficacy is unaffected by pus, serum or tissue fluid (organic matter) but is increased in alkaline medium; (solution) of strength 1:1000 in isotonic saline is used in treatment of infected wounds and burns, 2% pessary in vaginitis and cervicitis.

Triphenylmethane dyes: Gentian violet (crystal violet, aniline dye, or medicinal gentian violet)

These dyes are toxic against gram-positive organisms and fungi. Specifically effective against *Staphylococci*, *C. diphtheriae* and *P. pyocyaneus*. Only disadvantage is the staining of skin and mucus membrane. It is a non-irritant and potent antiseptic. It is used in the form of jelly or lotion (0.5-1%) for application on burns and for the treatment of various disinfections of skin, i.e. furunculosis, boils, chronic ulcers, infected eczema, thrush, impetigo, ringworm and mycotic infections, etc. Gentian violet can also be used in the treatment of strongyloidosis and oxyuriasis on oral administration.

Brilliant green: It also acts as an antiseptic and disinfectant like gentian violet. Used as a 0.05-1% solution in water or hypertonic saline in the treatment of burns, impetigo and infected wounds.

Triple dye lotion: It contains gentian violet 0.25% + brilliant green 0.25% + acriflavine or proflavine 0.1%. It is used as first aid treatment for burns.

Methylene blue: It is used systemically in cyanide poisoning as it converts methaemoglobin to hemoglobin.

Heavy Metals

Mercury compounds: They are bacteriostatic, but are ineffective against spores. They act by precipitating proteins and by inhibiting sulphhydryl enzymes of bacteria.

- Mercuric chloride
- Used for sterilizing the skin and mucus membrane in a dilution of 1:1000.

Silver compounds: Silver nitrate and colloidal silver preparations are used as antiseptics. They also have astringent and caustic properties. The reduced silver agents deposited and stain the tissues black therefore used as a marker ink during voting.

- **Silver nitrate** kills microbes rapidly and the action is prolonged due to slow release of silver ions from *silver proteinate* that is formed by an interaction with tissue proteins. Used as a prophylaxis against **gonococcal ophthalmia neonatorum**.
- **Silver sulfadiazine** is also highly active against *Pseudomonas* and therefore is used in burn wounds.

- **Colloidal silver compound:** Slowly release silver. They are non-corrosive, non-irritant, non-astringent and have better penetrability used as nasal and eye drops.

Zinc salts: Zinc salts have mild antiseptic, astringent and corrosive properties. The action is probably due to precipitation of proteins by zinc ions. Zinc oxide (10%) can be used as an ointment or lotion in eczema, impetigo and psoriasis and varicose veins.

- Zinc chloride is used in dentistry as an astringent and a local analgesics.
- Solution of zinc sulphate (0.1% to 1.0%) is used as an antiseptic eye drops.

Antiseptics/Disinfectants: Dental uses

- Sterilization of surgical instruments.
- Preparation of skin/mucous membrane prior to surgery.
- For irrigation of root canal in endodontics.
- Cleaning of surgical (operating) areas.
- As an ingredient of dentifrices and mouth washes.
- For inhibition of dental plaque formation.

Vaccines and Antisera

HISTORY

Edward Jenner (1798) : Discovered the vaccine against small pox. He was the pioneer, in introducing the therapy with vaccines and sera. Other landmarks in the history of vaccination are:

- 1921 : BCG
- 1923 : Diphtheria
- 1923 : Pertussis
- 1927 : Tetanus
- 1957 : Sabin live oral polio vaccine
- 1960 : Measles vaccine

[Important six vaccines recommended in childhood by WHO]

Host defenses: The host defenses against the various infections may be local and systemic, specific and non specific, and cellular and humoral. A person is said to be in good health, when all these defense system works in balance and in overlapping pattern.

Specific defenses: Once, the pathogen have broken local defense mechanism, the role of specific defense mechanism comes into existence, under the influence of which, the antigenic material (pathogen) is being recognized, destroyed and eliminated from the host body.

IMMUNITY

Immunity is the state of relative resistance to disease, which develops after exposure to the specific antigen (agent) responsible for infection. A person is said to be immune when he possesses “specific protective antibodies or cellular immunity as a result of previous infection or immunization”. The specific defense mechanism (immunity) can be discussed under the headings of a) Active immunity and b) Passive immunity.

Active immunity: The immunity which is developed in an individual as a result of any infection or by specific immunization is called active immunity. It is generally associated with presence of antibodies or cells having specific action on the microorganisms.

Active immunity may be acquired either by:

- Clinical infection, e.g. chickenpox, measles, etc.
- Sub-clinical infections like; polio and diphtheria.

Or by administering:

- Living organisms
- Dead or killed organisms, e.g. *enteric fever* and *whooping cough*.
- Attenuated or treated organisms, e.g. *small pox* and *rabies*.
- Separated exotoxins, e.g. *scarlet fever*.
- Toxoids or modified toxins, e.g. *diphtheria* and *tetanus*.

Important Terminologies

• Responses to immunization

a. Primary response: After first time administration of antigen in an animal or human, there occur rise in the level of antibody titer within few days (after latent period). This is specifically **IgM** antibody. The important outcome of primary antigenic challenge is education (sensitization) of Reticulo-endothelial System of the body. There occur production of what are known as “**memory cells**” or “**primed cells**” by both T and B lymphocytes.

b. Secondary (booster) response: The response of secondary or booster dose leads to production of both **IgM and IgG**. The secondary response is characterized by:

- More rapid production of antibody
- Shorter latent period

- Antibody titer is very high
- Antibody response remain their for longer period of time.

• Humoral and cellular immunity

Humoral immunity: Humoral immunity comes from the B-cells (bone marrow derived lymphocytes), which proliferate and produces specific antibodies. Five different types of Immunoglobulins are produced, i.e. IgG, IgM, IgA, IgD and IgE; each class representing a different functional group. These antibodies circulate in the body and act directly by neutralizing the microbes, or its toxin or making the microbes (more) susceptible to attack by the polymorpho-nuclear monocytes.

Cellular immunity: Cellular immunity plays a significant role in defending our body against infections. It is mediated by the T cells which differentiate into sub-groups able to help B-lymphocytes. The T cells do not produces antibody, but they are responsible for the re-organization of antigen on contact with antigen, the T cells initiate a series of responses, e.g. activation of macrophages, release of cytotoxic factors, release of chemotactic chemicals, mononuclear inflammatory reactions, delayed hypersensitivity reactions, secretions of immunological mediators, etc.

Passive immunity: When antibodies produced in one person (human or animal) and then transferred to another

person (human), in order to protect him from any infectious disease, is called as passive immunity or it can be defined in other words, the body does not produce its own antibodies but depends upon the ready-made antibodies (produced in other living being)

Passive immunity can be induced by:

- Administering antibody (immuno-globulin or antiserum) containing preparation.
- Transferring antibody from mother to fetus through placenta. Human milk also contain some protective antibodies (IgA).
- Directly by transferring lymphocytes into the host, to induce passive cellular immunity.

Characteristics of Passive Immunity

- It provides only temporary immunity (only days to month).
- Immunity is rapidly developed.
- There is no training (sensitization) of reticulo-endothelial cells to produce antibody on second time or reinfection (Table 15.3.1).

IMMUNIZING AGENTS

Vaccines: Vaccines are the immuno-biological substances designed to produce specific protection against a specific disease by mean of a protective antibody or other immune mechanism. Vaccines are made from microorganisms like: bacteria, viruses, and rickettsia; responsible for various diseases.

Table 15.3.1: Passive Immunity

Passive immunization (antisera)	Indications [Prophylaxis and treatment]	Dose and route of administration
Diphtheria antitoxin (horse)	Diphtheria	500 to 1000 IU, IM
Rabies Immunoglobulin (horse)	Rabies	20 IU/kg/IM/apply half dose locally on/ around the wound
[within 72 or atleast 24 hrs]		
Antirabies Serum (ARS, horse)	Rabies	40 IU/kg/IM apply half dose locally on/around the wound
[within 72 or atleast 24 hrs]		
Tetanus Immunoglobulin (human)	Tetanus	Prophylactic: 2500 IU/IM Therapeutic : 3000 – 6000 IU/IM
Tetanus antitoxin (ATS) horse	Tetanus	Prophylactic: 1500 IU/IM/SC Therapeutic: > 50,000 IU/IM/SC
[In case of non availability of Ig]		
Botulinum antitoxin (polyvalent, horse)	Botulism	1000 IU/IM/every 3 to 4 hours
Gas gangrene (AGS, horse)	Gas gangrene	10,000 IU: Cl. welchii antitoxin
[Polyvalent]		5,000 IU : Cl. septicum antitoxin
		10,000 IU: Cl. oedematiens antitoxin
		[Combination of all above antitoxin should be administered IM, SC and IV]
Antisnake venom	Snake bite	20-30 ml can be given within -
polyvalent (horse)	cobra, viper, krait	24 hours of snake bite, additional - doses may be required

Toxoids: They are prepared from the exotoxins of the bacteria by treatment with formaldehyde followed by purification. By this process exotoxins lose their toxicity but retain or maintain its antigenic specificity for the active toxin.

Immunization (Table 15.3.2)

Active immunization: It is the administration of antigen to the host in order to induce antibody production. Vaccines are used for active immunization. Vaccines are suspensions of microorganisms (dead or live attenuated) which stimulate the immunity, which takes sometime to develop and therefore used prophylactically. The antibodies so developed destroy the specific microorganism when it enters the body. It can be subdivided into:

a. Primary immunization provides primary immunity and is usually given in children, e.g. DPT (triple antigen given to infants), BCG, etc.

b. Secondary immunization is done to reinforce the primary immunity by giving **booster doses**.

Table: Immunizing Agents:

Vaccines

- Live attenuated vaccines:
 - Bacterial: BCG, Typhoid oral and Plaque.
 - Viral: Oral polio, yellow fever, mumps, measles, rubella Influenza, etc.
 - Rickettsial : Epi Typhus (1st times)
- Inactivated or killed vaccines:
 - Bacterial: Typhoid, cholera, pertussis, meningitis, etc.
 - Viral: Rabis, salk, influenza, encephalitis, hepatitis B.
- Toxoid : Bacterial: Diphtheria and tetanus.

Table 15.3.2: National immunization schedule

Age	Vaccine	No. of doses	Route of administration
6 weeks	DPT	3	Intramuscular
to 9 months	Polio	3	Oral
	BCG	1*	Intradermal (.05 ml)
9 months to 12 months	Measles		Subcutaneous (0.5 ml)
16-24 months	DPT	1**	Intramuscular
	Polio	1**	Oral
5-6 years	DT	1@	Intramuscular
	Typhoid	2	Subcutaneous
16 years	Tetanus toxoid	1@	Intramuscular
	Typhoid	1@	Subcutaneous
Pregnant woman (16-36 weeks)	Tetanus toxoid	1@	Intramuscular

* For institutional deliveries, BCG should be given at birth.

** Booster dose

@ 2 doses, if not vaccinated previously.

Note

1. Interval between 2 doses should not be less than 1 month.
2. Minor coughs and colds and mild fever are not a contraindications to vaccination.

Vaccines in Common Use and Their Recommend Schedules

Bacterial Vaccines

1. BCG (Bacillus of calmette and guerin) Vaccine

- Protection against Tuberculosis
- Organism involved *Mycobacterium tuberculosis*
- Type of agent Live attenuated
- Type of immunization Active immunization
 - Dose and Route of administration
 - 0.1 ml, Percutaneous (old method)
 - 0.0001 to 0.001 ml, Intradermal (tuberculine)
 - 0.02 to 5 mcg, Intradermal (purified protein derivative of tuberculine)

- Primary immunization At birth
- Booster dose 7 and 14 years
- Indications In all children.

MONTOUX TEST

- Site – forearm
- Route – intradermal injection
- Material – OT (tuberculin)
– PPD (5 U, PPD)
- Dose – 0.1ml (IU of PPD in 0.1ml)
- Result – Positive reaction within 12-72 hours characterized by erythma and indurating edema.

Erythma reaction (Indurations) Grade

+	< 5 MM	–ve
+	about 5 mm	–ve/+ve
+	6-10 mm	+ve
+	11-20 mm	+ +ve
+	>20 mm	+ + +ve

2. Diphtheria Vaccine [constituent of DPT and DT]

- Protection against Diphtheria
- Organism involved *Corynebacterium diphtheriae*
- Type of agent Toxoid
- Type of immunization Active immunization [Diphtheria toxoid]
– Dose and route of administration 0.5 to 1.0 ml SC injection, toxoid : 0.5 to 1.0 ml IM
- Type of immunization Passive immunization [Diphtheria anti-toxin]
– Dose and route of administration
– Prophylactic: 1000 to 10,000 IU
– Therapeutic: 20,000-40,000 IU, IM or IV
- Diagnostic test Schicks test
- Primary immunization 6, 10, 14th week of age
- Booster 18 month and at 4-6 years
- Indications For all children

3. Pertussis Vaccine [constituent of DPT]

- Protection against Pertussis
- Organism involved *Bordetella Pertussis*
- Type of agent Inactivated
- Type of immunization Active immunization
– Dose and route of administration 3 injections, (20,000 million in 0.5 ml ampule)
at least 4 weeks apart, SC.
Passive immunization [pertussis immunoglobulin]
Prophylactic: 1 or 2 injections at 1 week interval, IM
Therapeutic: 2 injections at 1 week interval, IM
- Primary immunization 6, 10 and 12 weeks of age
- Booster 18 months and 4-6 years.
- Indications For all children.

4. Tetanus Vaccine [constituent of DPT]

- Protection against Tetanus
- Organism involved *Clostridium tetani*
- Type of agent Toxoid

- Type of immunization
 - Dose and route of administration
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

Active immunization [Tetanus Toxoid]: TT
 3 injections, 0.5 ml at least 4 weeks apart, IM/SC
 Passive immunization [Tetanus antitoxin]
Prophylactic: 1500 to 10,000 U : IM/SC
Therapeutic: 10,000 to 100,000 U : IM/SC
 6, 10 and 14th weeks of age
 18 months and at 4-6 years

- For all children
- Adults: Postexposure prophylaxis if > 5 years has passed since last exposure (0.5 ml) IM/SC

5. Cholera Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

Cholera
Vibrio cholerae
 Inactivated
 Active immunization
 0.5 ml, SC or IM, repeat 1 ml after 7 days,
 (1 ml containing 8×10^9 organisms)
 Adults: 2 doses, 1 month apart
 Every 6 months (0.5 ml)
 People living in endemic regions.

6. Typhoid/Paratyphoid A, B (TAB) Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

Typhoid
Salmonella typhi/*S. paratyphi A and B*
 [1 ml contain - 1×10^9 *S. typhi*]
 [1 ml contain - 7.5×10^8 *S. paratyphi*]
 Inactivated
 Active immunization
 3 injections, (0.5 ml) SC at least 7 days apart. (interval)
 After 3 years at any age, 2 doses 4 weeks apart.
 Every 3 years
 Risk of exposure to typhoid fever.

7. Typhus Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

Typhus fever
Rickettsia prowazekii
 Inactivated
 Active immunization
 2 injections, 1 ml SC, at least 7 days apart
 After 3 years at any age
 every 3 years
 Risk of exposure to typhus fever.

8. Plague Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration

Plague
Pasteurella pestis
 Inactivated.
 Active immunization
 0.5–1 ml, two doses at an interval of 7 to 14 days, SC or IM.
 (1 ml contain - 2×10^9 organisms)

- Primary immunization
- Booster
- Indications

9. Botulism Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

Single dose
6 month (if required)
In an epidemic.

Botulism
Clostridium botulinum
Antitoxin
Passive immunization
Prophylactic: 2500 U botulinum antotoxin IM or IV
Therapeutic : 10,000 U to 50,000 U IM or IV
Once
When required
Risk of exposure

Viral Vaccines

1. Poliomyelitis Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

Poliomyelitis
Various strains of polio virus (type 1, 2, 3)
Live virus
Active immunization
OPV, monovalent and trivalent, (0.5 ml) oral directly
or diluted with milk or water.
0, 6, 10 and 14th weeks of age
18 months, again at 4 to 6 years
In all children.

2. MMR Vaccine (Trimovax or Tresivac)

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Type of immunization
 - Dose and Route of administration
- Primary immunization
- Booster
- Indications

[Measles, Mumps and Rubella]

MMR groups of viruses
Live virus,
Active immunization
- 0.5 ml, SC or IM
Passive immunization
0.22 ml/kg SC/IM Mumps Ig (Immunoglobulin),
12-15 months
11-12 years
In all children.

3. Hepatitis A Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

Hepatitis A

Hepatitis A virus
Inactivated virus
Passive immunization
Immunoglobulin (Ig) : 3.5 to 8 mg / kg body weight, IM
Single dose before traveling in endemic region.
After 6 to 12 months
For all children, Pre and Postexposure prophylaxis,

4. Hepatitis B Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

5. Influenza Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

6. Rabies Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

7. Varicella Vaccine

- Protection against
- Organism involved
- Type of agent
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

8. Yellow fever Vaccine

- Protection against
- Organism involved

Hepatitis B*Hepatitis B virus*

Inactive viral antigen

Passive immunization

Hepatitis B immune globulin human : 0.06 ml / kg body weight as soon as possible, IM on gluteal or deltoid region, avoid IV route.

At Birth, 1 month, 6 to 18 months after 5 years (if needed)

For all children, post-exposure prophylaxis, hemophiliacs and persons with occupational risk.

Influenza

Various strains of influenza virus (Influenza A and B viruses)

Inactivated viruses

Active immunization

2 injections of 1 ml at least 2 months apart, SC

Single dose

Yearly

High risk people like Asthmatics

Rabies

*Various strains of rabies viruses**Inactivated virus*

Active immunization

2 ml of 5% suspension, SC

On pre-exposure: 3 doses at days 0, 7, and 21 days.

On post-exposure: 6 doses: 0, 3, 7, 14, 30 and 90 days.

Passive immunization

Antirabies serum: 20 IU/lb or 40 IU/kg of body weight, IM

On exposure/prophylactically

After 1 year, followed by; 2 to 5 years regularly.

Prophylactic in contact person or in post-exposure treatment

Herpes

Varicella group of viruses

Live virus

Active immunization

2 doses, 4-6 weeks apart at 18 month.

At 18th month of age.

-

In all children in between (18 months to 13 years of age) with no history.

Yellow fever
virus

- Type of agent
- Type of immunization
 - Dose and route of administration
- Primary immunization
- Booster
- Indications

17 D vaccin (live virus)
 Active immunization
 Yellow fever vaccine (17 D), 0.5 ml, SC
 As and when needed.
 10 years
 Travellers/laboratory persons.

Passive immunization: It is the process of imparting immunity to a host passively by the transfer of antibodies, e.g. antisera and immunoglobulins (Ig). This affords immediate protection as readymade antibodies are available. Antisera like tetanus antitoxin, gas gangrene antitoxin, diphtheria and antirabies serum are obtained from serum of horses which are actively immunized against the specific organism. Sensitivity tests should be done before giving antisera.

IMMUNOGLOBULINS

Immunoglobulins (Ig): Immunoglobulin are human gamma globulins that carry the antibodies- like normal human gamma globulin, tetanus Ig, rabies Ig, anti-diphtheria Ig and hepatitis-B Ig. Allergic reaction including serum sickness and anaphylaxis can occur with antiserum, while it is uncommon with Igs.

Human Immunoglobulins

- Human normal Ig: Hepatitis A, measles, rabies, tetanus mumps, etc.
- Human specific Ig: Hepatitis B, varicella, diphtheria, etc.

Antisera

- Bacterial: Gas gangrene, botulism, tetanus and diphtheria.
- Viral: Rabies, etc.

Antisera or antitoxins

- If the animals used as sources for immune sera. They are actively immunized by bacterial cells, the sera contain antibodies which agglutinates, clamp, lyse or kill the organisms (bacteria), making them inefficient. Such a serum is called as antibacterial serum or **anti-serum**.
- On the other hand if , the toxins are used to actively immunized animals, the antiserum produced neutralizes the toxins rendering them ineffective. Such a serum is called antitoxic serum or **antitoxins**.

Hazards of Immunization

- There may be local general reactions like; fever, malaise, headache, etc.

- There may be reactions due to faulty techniques of; production of vaccine, and procedure of administration of vaccine, i.e. improper route, inadequate or over dose of the vaccine, wrong dilution, etc.
- Reaction due to **hypersensitivity**; specifically on administration of antisera and antitoxin.
- It may lead to development of certain neurological manifestations; post-vaccinal encephalitis and encephalopathy following anti-rabies and small pox vaccination, Guillain – Barre Syndrome following influenza vaccination.
- Provocative reactions: development of a disease which is totally unrelated to immunizing agent, e.g. provocative polio after APT administration against diphtheria, etc.

Precautions to be taken

- There should be proper sterilization of needle, syringe. Proper and right selection of subject and object.
- Carryout proper sensitivity test before administering antiserum and antitoxin.
- Adrenalin (1:1000 solution) should be kept ready, in case of anaphylactic reaction, administered 0.5 ml of adrenaline solution IM, immediately.
- An injection of antihistaminic (10-20 mg of chlorpheniramine maleate) should also be kept ready and administered it as and when needed.
- Measles and BCG vaccine should be reconstituted only with the diluents supplied by the manufacturers and should be reconstituted only as and when needed, i.e. solution should never retained for use in subsequent session.
- Careful investigation and management should be done when adverse effect occurs.

STORAGE OF VACCINES

Cold chain: It is a system of storing and transporting vaccines at lower temperature from the manufacturer to the actual vaccinating location, so that their potency and efficacy should be preserved.

Cold box: This can transport large quantity of Vaccines.

- No drug should be kept in freezer.

a. Uppermost compartment of freez contains:

- RMP

R = Rabies

M = Measals (MMR)

P = Polio (Oral)

(Stored at 0-4 degree centigrade temperature)

b. Middle compartment of freez contains:

- DDT

D = DPT

D = DT

T = TLT

(Stored at 4-10 degree centigrade temperature)

Nutrients and Vitamins

NUTRIENTS

- a. Micronutrients: They include; vitamins and minerals
- b. Macronutrients: They include:

Protein	:	7 to 15%
Carbohydrate	:	65 to 80%
Fat	:	10 to 30%

Six Vital Components of Food

MINERALS

These are the chemical elements which are found in human body, and are required for growth, repair and regulation of vital body functions. They can be subdivided into

- a. **Major minerals:** It includes calcium, phosphorus, sodium, potassium and magnesium.
- b. **Trace elements:** These are the elements required by the body in very small (trace) amount, i.e. only few (mg)/day. They includes iron, iodine, fluorine, zinc, copper, cobalt, chromium, manganese, molybdenum, selenium, nickel, tin, silicon and vanadium.

VITAMINS

Vitamins are the organic compounds which are classified under essential nutrients. They are required by the body in very small amounts (micronutrients) and are used in numerous cell activities; vitamins do not yields energy but they aid the release of energy from glucose and assist growth and repair mechanisms.

FIBERS

Fibers are the non starch polysaccharides. They are present in vegetables, fruits and grains. They regulates cell metabolism by influencing the digestion and absorption of other energy –producing nutrients. They absorb water, swells and increases the gut motility. Other significant physiological roles of fibers are:

- Cholesterol lowering effect.

- Weight reduction
- Reduces incidences of Myocardial Infarction, diabetes, hypertension, bowel diseases and cancer.

CARBOHYDRATES

They are the basic sources of energy and third major component of food. There are three main sources of carbohydrates a) Starch b) Sugars and c) Cellulose. Carbohydrates are broken down to provide energy. They are the ideal food to eat before exercise. They are also act as “Protein sparer” as they prevent protein from undergoing oxidation process to provide energy.

FATS

They are the stored form of energy and richest calories suppliers. They provide energy during emergent conditions of severe deficiency of energy, e.g. during long starvation. They also help in formation of chemical messengers, such as hormones and prostaglandins. They also plays a significant role in GIT for the absorption of fat soluble vitamins (Vit. A, D, E, K).

PROTEINS

Proteins are the complex organic nitrogenous compounds. They are basically composed of carbon, hydrogen, nitrogen, oxygen, and sulphur in varying amount. Amino acids, released from the digestion of proteins, are used as building blocks in the formation of new cells and tissues. They are needed by the body for:

- Body building
- Repair and maintenances of body tissues.
- Maintenance of osmotic pressure and
- Synthesis of certain substances like; antibodies, plasma proteins, enzymes, hormones, and coagulation factors.

MINERALS

In the same way as **vitamins** play a major role in keeping the body healthy, **minerals** are vital material in the human body, stimulating growth and maintaining good health. Minerals also can be subject to abuses such as excessive intake.

Iron and calcium are recognized as the two important minerals, especially for the pregnant women. **Calcium and phosphorous** are needed for bone and teeth. Iron is a vital part of hemoglobin. The thyroid gland need iodine. Sodium, potassium, magnesium, chloride, bromide, fluoride, copper, cobalt, zinc and manganese are among the minerals required in much smaller quantities therefore known as trace elements.

Optimum health can be maintained by a balanced diet in which minerals occur naturally. With most minerals the absorption rate from food eaten averages between 10 to 15%. Where as sodium, potassium and chloride were completely absorbed.

Taking more than is actually expensive and wasteful, since the body excretes what is unnecessary.

The Vitamins: The vitamins are essential micronutrients of diet, which do not give energy but are necessary for the normal metabolism of the body. They are organic compounds and were thought to be “vital amines” and named by Funk as **vitamine**.

This term today is retained as **vitamin**. Most of the vitamins can be synthesized today. Adequate amounts reach the body via a well balanced diet. Deficiencies may occur on restricted diets, malabsorption syndromes, or in states where body need increases, e.g. during body growth, pregnancy and lactation. Thus, vitamin deficiency states can develop due to: inadequate diet, impaired absorption, increased requirement, and increased rate of excretion.

Many vitamins often as “**Multivitamins**” are administered as “**Tonics**” with mineral or other dietary supplements. For such purposes, large doses are used. There is little justification for such an use. Efforts should be made to avoid indiscriminate vitamin therapy. *Not all vitamins are harmless. The toxic effect of vitamin A and vitamin D especially in infant and children must always be kept in mind.*

Classification

- **Fat soluble vitamins:** Vitamins A, D, E and K.
- **Water soluble vitamins:** Vitamins B (B complex) and C.

FAT SOLUBLE VITAMINS

Vitamin A (carotene, carotenoids): Vitamin A is present in the diet as retinol, dehydrorretinol or as

carotenoids. Carotenoids are pigments present in green yellow vegetables and fruits and is converted in the body to retinol.

Functions: Vitamin A is essential for the body. It assist in the body growth and in the metabolism of body. Protects body against infection. Vitamin A is essential for maintenance of the integrity of epithelial cells, for growth and cell-mediated immunity, in the formation of skin and mucous membrane, especially of eyes (cornea and retina). It is also essential for the synthesis of rhodopsin, the photosensitive pigment of rods. They have an important role in dark adaptation.

Major dietary sources: Fish liver oil, egg yolk, milk, butter, green and yellow pigmented vegetables, tomatoes, fortified foods, yellow pigmented fruits, i.e. mango, papaya, etc.

Recommended Dietary Allowances (RDAs)

- **Children :** 2000-3500 IU
- **Males :** 5000 IU
- **Females :** 4000 IU

Main deficiency disorders

1. Night blindness (Nictalopia)
2. Xerophthalmia (dryness of the eyes) and Bitots spot.
3. Keratomalacia: liquifaction of the cornea.
4. Hyperkeratosis of the skin
5. Increase susceptibility to cold, influenza and infections
6. Keratinization of epithelial tissue

Therapeutic doses

- **Oral** 25,000-100,000 IU
- **Parenteral** 50,000 IU/IM

Uses

- In the prophylaxis and treatment of vitamin A deficiency.
- Acne- Retinoic acid or synthetic analogs of vitamin A like tretinoin or isotretinoin are used.

Hypervitaminosis A: Since vitamin A is a fat-soluble vitamin, it accumulates in the body on prolonged administration. The symptoms are dry skin (hyperkeratosis), anorexia, fever, alopecia, anemia, edema, headache, skin ulcers and tenderness over the bones.

Vitamin D (Calciferol): Vitamin D, a fat-soluble vitamin, is a (pre formed) hormone produced in the skin from 7-dehydrocholesterol under the ultraviolet rays. It is converted into active metabolites in the body which regulate **plasma calcium** levels and various function of the cells.

Forms of Vitamin D in man

- **Ergocalciferol** (vitamin D₂) from plants.
- **Cholecalciferol** (vitamin D₃) synthesized in the skin from 7-dehydrocholesterol.

Cholecalciferol (Vitamin D₃) is converted to 25-OHD₃ (calcifediol) in the liver which is in turn converted to 1,25-dihydroxycholecalciferol (calcitriol) in the kidney. Calcitriol is the active form of vit D while calcifediol is the main metabolite in circulation. Conversion of calcifediol to calcitriol is influenced by plasma phosphate concentration and by PTH (Fig. 15.4.1).

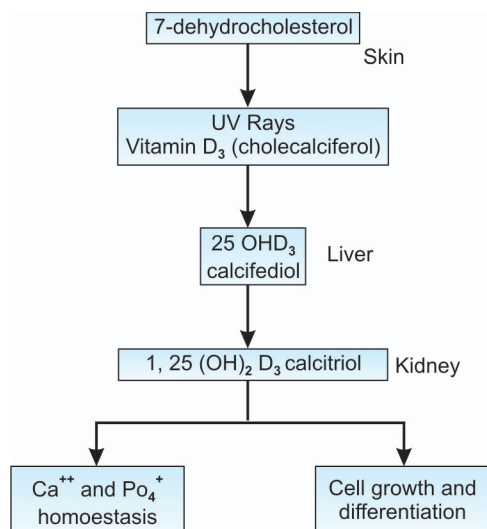


Fig. 15.4.1: Synthesis of vitamin D₃

Functions: It Assists in the body growth and regulates the calcium and phosphorous metabolism of the body. (Bones and teeth)

Table: Functions of Vitamin D and its metabolites

- **Bone:** Enhance bone resorption, stimulate normal mineralization.
- **Intestine:** Promotes intestinal absorption of calcium and phosphorus.
- **Kidney:** Increases tubular reabsorption of phosphate and variable effect on reabsorption of calcium.
- **Others:** Permits normal growth.

Major dietary sources: Fish (shark) liver oil, egg yolk, milk whole, butter, margarine, salmon, sardines, etc.

Recommended Dietary Allowances (RDAs)

- **Children** 400 IU
- **Males** 200-400 IU
- **Females** 200-400 IU

Main deficiency disorders

1. Rickets (bowing of the legs).
2. Osteomalacia (softening of the bones)

3. Osteoporosis (pores in the bones)
4. Infantile tetany

Therapeutic doses

• Oral

Ergocalciferol	50,000-500,000 IU
Cholecalciferol	400-1000 IU
Calcitriol	0.5-1 microgram/day
Calcifediol	300-350 microgram/week

• Parenteral

Ergocalciferol	50,000-200,000 IU/IM
Calcitriol	1.2 microgram IM

Uses

- In the treatment of nutritional rickets and osteomalacia.
- Vitamin D resistant rickets is a hereditary disorder with abnormality in renal phosphate reabsorption. *Phosphate with vitamin D is found to be useful.*
- Vitamin D dependent rickets is due to calcitriol deficiency (inability to convert calcifediol to calcitriol) and is treated with **calcitriol**.
- Vitamin D may have many anticancer properties and may be especially helpful against breast and colon cancer.
- In treatment of senile osteoporosis oral vitamin D supplements with calcium may be tried.
- In management of hypoparathyroidism : Calcitriol with Ca⁺⁺ supplements are beneficial.

Adverse reactions: High doses of vitamin D used for long periods result in hypervitaminosis D manifesting as:

- Generalized decalcification of the bones,
- Hypercalcemia,
- Hyperphosphatemia resulting in weakness, drowsiness, nausea, abdominal pain, thirst, renal stones and hypertension.
- Hypervitaminosis D in children is most often due to unnecessary vitamin D supplementation by parents.

Vitamin E (Tocopherols)

Functions: Vitamin E (tocopherols) has large number of functions, such as assisting cell respiration, assisting in the metabolism of fat and carbohydrates, in reproduction, in manufacturing connective tissue in the muscles.

Vitamin E acts as an anti-oxidant. It prevents the damage due to free radicals in normal metabolic reactions and probably in this manner give the body greater resistance and resilience. It is also essential for normal structure and function of the nervous system. It is also required to maintain the integrity of the biological membranes. The Alfa tocopherol is biologically most potent amongst other tocopherols.

Major dietary sources: Wheat germ, vegetable oil, green leafy vegetables, nuts, cereals, eggs, dairy products, etc.

Recommended Dietary Allowances (RDAs)

- **Children** 7-10 IU
- **Males** 12-15 IU
- **Females** 12 IU

Main deficiency disorders

1. Deficiency in animal produces
 - Sterility
 - Loss of embryo
 - Muscular dystrophy and paralysis.
 - Degenerative changes in the spinal cord and heart
2. Deficiency state not established in humans, possibly causes
 - Hemolytic anemia
 - Muscular lesions
 - Creatinuria

Therapeutic doses

- **Oral**

d- alfa Tocopherol	10-200 mg
Tocopherol mixed concentrate	10-200 mg
d-alfa Tocopherol acetate concentrate	10-200 mg
- **Parenteral**

Tocopherol mixed concentrate	10-200 mg IM
d-alfa Tocopherol acetate concentrate	10-200 mg IM

Uses

- It has been tried in G-6-PD deficiency (hemolytic anemia)
- In the treatment of sterility and menopausal syndrome and other conditions with no definite evidence of obvious benefit, i.e.
 - Muscular lesions,
 - Creatinuria

Vitamin K (phylloquinone): It is a fat-soluble vitamin, which is essential for the biosynthesis of certain clotting factors. Principally they are of three types:

- Vitamin K₁ [Phylloquinone]: It is present mainly in fresh green (dark green) vegetables.
- Vitamin K₂ [Menaquinone]: produced in the gut by bacteria (normal intestinal flora) and
- Vitamin K₃ [Menadione]: a synthetic compound used therapeutically.

Functions: Vitamin K is required for the normal blood clotting. It stimulates the production or biosynthesis and/or release of certain coagulation factors **prothrombin** and factors **VII, IX and X** by the liver. It is stored in liver.

Major dietary sources: Green leafy vegetables, liver, cheese, egg yolk, tomatoes, cereals, etc. Cow milk is

richer source of vitamin K (60 mcg/L) than human milk (15 mcg/L).

Recommended Dietary Allowances (RDAs)

- **Children** Extremely small
- **Males** Approximately 0.03 mg/kg
- **Females** ?

Main deficiency disorders

1. Hemorrhagic tendencies i.e. epistaxis, bleeding gums, etc.
2. Hypoprothrombinemia.

Therapeutic doses

- **Oral**

Menadione sodium diphosphate:	5 mg
Menadione sodium bisulfite:	2-5 mg
- **Parenteral**

Menadione sodium diphosphate:	5-75 mg IM or SC.
Menadione sodium bisulfite:	2-5 mg IM or SC.

Adverse effect: Adverse reactions are seen on parenteral administration – allergic reactions and jaundice can occur.

Uses

- In the treatment of vitamin K deficiency
- Newborn babies lack intestinal flora and have low levels of prothrombin and other clotting factors. Routine administration of vitamin K – 1 mg IM prevents hemorrhagic disease of the newborn.
- In the treatment of oral anticoagulant poisoning.

WATER SOLUBLE VITAMINS

Vitamin B Complex: This group of vitamins include thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, biotin and cyanocobalamin.

Vitamin B₁ (Thiamine)

Functions: Allow the body to use carbohydrates (starch and sugar). Physiological role: Thiamine is converted to thiamine pyrophosphate, which acts as a coenzyme in carbohydrate metabolism. Necessary for the normal functioning of the nerves, heart and GIT.

Major dietary sources: Liver, whole grain, enriched bread, cereals specially outer layers, i.e rice polishing, pork, egg yolk, nuts, and meat.

Recommended Dietary Allowances (RDAs)

- **Children** 0.7-1.2 mg
- **Males** 1.2-1.4 mg
- **Females** 1.0-1.1 mg

Main deficiency disorders

1. **Beriberi:** They are of three types a) the **dry** form characterized by peripheral neuritis b) the **wet** form

characterized by heart involvement and c) the **infantile** beriberi, seen in infants.

2. **Wernick's encephalopathy:** Characterized by ophthalmoplegia, polyneuritis, ataxia and mental deterioration.
3. **Korsakoff's psychosis** are also thought to be due to thiamine deficiency.
4. **Anorexia**
5. **Constipation**

Therapeutic doses

- **Oral** 5-100 mg
- **Parenteral** 5-100 mg IM, IV

Vitamin B₂ (Riboflavine)

Functions: It is necessary for the development and functioning of skin, eyes and mucous membrane. Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) containing the active form of riboflavin are coenzymes in various oxidation-reduction reactions. It is also used for the metabolism of starch and protein.

Major dietary sources: Organ meats, milk, eggs, green vegetables, grains and enriched bread.

Recommended Dietary Allowances (RDAs)

- **Children** 0.8-1.4 mg
- **Males** 1.4-1.7 mg
- **Females** 1.2-1.3 mg

Main deficiency disorders

1. Stomatitis
2. Glossitis
3. Facial dermatitis
4. Photophobia
5. Cheilosis
6. Corneal vascularization etc.

Therapeutic doses

- **Oral** 1-5 mg
- **Parenteral** 1-10 mg parenteral, (IM)

Vitamin B₃ (Niacin or Nicotinic Acid)

Functions: Necessary for the metabolism of starch, fat and protein. Nicotinic acid is converted to **nicotinamide**. Nicotinamide adenine nucleotide (NAD) and its phosphate (NADP) are coenzymes which are involved in several oxidation-reduction reactions.

Nicotinic acid is also a lipid-lowering agent and it is also needed for normal blood formation and normal functioning of the nervous system, skin and mucous membranes.

Major dietary sources: Liver, fish, poultry, red meat, enriched bread, cereals, rice polishings, bran, etc.

Recommended Dietary Allowances (RDAs)

- **Children** 9-16 mg
- **Males** 16-19 mg
- **Females** 13-15 mg

Main deficiency disorders

Pellagra which is characterized by 3D disorder:

- Dementia
- Diarrhea
- Dermatitis and other manifestations like,
- Nervousness, insomnia and confusion.
- Pigmentation of the skin,
- Stomatitis and glossitis,
- Headache, hallucinations, and
- Megaloblastic anemia, etc.

Therapeutic doses

- **Oral** 20-50 mg
- **Parenteral** 20-50 mg

Vitamin B₅ (Pantothenic acid)

Functions: It has a large range of functions, pantothenic acid is converted to coenzyme A which is involved in several metabolic reactions including metabolism of food especially protein and fats. It affects the functioning of the skin, mucous linings and the hair. It protects body against infections. It has a function in assisting the liver and suprarenal glands. It also helps in formation of blood pigments. Calcium pantothenate is a component of multivitamin preparations.

Major dietary sources: Organ meat, egg yolk, peanuts, whole grains, cauliflowers, rice polishings, etc.

Recommended Dietary Allowances (RDAs)

- **Children** 2-4 mg
- **Males** 4-7 mg
- **Females** 4-7 mg

Main deficiency disorders

1. "Burning foot" syndrome
2. Weakness and fatigue
3. Mood fluctuation
4. Dizziness.

Therapeutic doses

- **Oral** 20-100 mg
- **Parenteral** 200-250 mg IM

Vitamin B₆ (Pyridoxine)

Functions: It is essential for human nutrition. Pyridoxal phosphate is a coenzyme involved in the synthesis of several amino acids, biogenic amines and other compounds like GABA and is involved in the metabolism of protein. It is needed for growth and normal functioning of blood cells.

Major dietary sources: Yeast, red meat, liver, whole grains, soyabeans, green vegetables.

Recommended Dietary Allowances (RDAs)

- **Children** 0.9-1.6 mg
- **Males** 1.8-2.2 mg
- **Females** 1.8-2.0 mg

Main deficiency disorders

1. Glossitis, stomatitis and cheilosis
2. Anemia, dermatitis
3. CNS Lesions i.e. peripheral neuritis,
4. Epileptiform convulsions in the children with low seizure threshold due to decreased GABA levels in the brain.

Therapeutic doses

- **Oral** 5-100 mg
- **Parenteral** 5-100 mg Parenteral. (IM)

Uses

1. In the prophylaxis and treatment of **pyridoxine deficiency**.
2. INH (Isoniazide) induced peripheral neuritis; pyridoxine is used both for prophylaxis and treatment.
3. Convulsions in infants due to pyridoxine deficiency.
4. '**Morning sickness**' in pregnancy-pyridoxine may reduce vomiting by an unknown mechanism.

Vitamin B₁₂ (Cyanocobalamin)

Functions: It is essential for normal functioning of the nervous system. It also helps in food absorption from the intestine. It is needed for normal blood formation.

Major dietary sources: Red meat, liver, milk, yolk, clams, etc.

Recommended Dietary Allowances (RDAs)

- **Children** 3 microgram (mcg)
- **Males** 3 microgram (mcg)
- **Females** 3 microgram (mcg)

Main deficiency disorders

1. Pernicious anemia
2. CNS lesions, paresthesias
3. Muscle in-coordination
4. Glossitis

Therapeutic doses

- **Oral** 10 mcg to 1 mg
- **Parenteral** 10 mcg to 1mg Parenteral.

Biotin: Biotin is a coenzyme in several metabolic reactions. It is an organic acid found in liver, nuts, egg yolk and other foods. Biotin deficiency in human is not known. Experimentally induced deficiency results in:

- Dermatitis
- Alopecia
- Anorexia
- Glossitis.

Vitamin C (Ascorbic Acid)

Functions: An enormous range of functions are attributed to vitamin C. These includes the activation of metabolism of cells and helps in absorption of iron. It is essential for collagen synthesis and therefore helpful in tissue repair. It gives increased protection against infections and helps the body detoxication system. It assists the skin tissue to develop normally, and play an important part in the tissues of the **bone and teeth**. It is necessary for the blood cell formation. It probably play a part in resisting viral infections of the body like common cold and AIDS, etc.

Major dietary sources: Citrus fruits like oranges, lemon, amla, lime, tomatoes, green vegetables, grapes, potato, green pepper, etc.

Recommended Dietary Allowances (RDAs)

- **Children** 45 mg
- **Males** 50-60 mg
- **Females** 50-60 mg

Main deficiency disorders

- Hemorrhages in subcutaneous tissues, **petechiae**, **ecchymoses** and impaired wound healings.
- **Scurvy:** Characterized by tender bleeding gums, deformed teeth, brittle bones, anemia and growth retardation.

Therapeutic doses

- **Oral** 100 mg to 1 g
- **Parenteral** 100 mg to 1g parenteral

Uses

1. Prevention of scurvy (prophylactic)—50-100 mg daily.
2. In the treatment of Scurvy
3. In the prevention (prophylaxis) of common cold—large doses (0.5-1.5 gm) of vitamin C has been tried .
4. Sometimes to acidify urine.

Note: Vitamin B₁₂ and Folic acid are discussed in chapter on hematinics.

Appendix

Essential Medicines — 15th edition (March 2007) WHO Model List

abacavir (ABC)	benzoic acid + salicylic acid
acetazolamide	benzoyl peroxide
acetylcysteine	benzoate
acetylsalicylic acid	benzyl penicillin
aciclovir	betamethasone
albendazole	biperiden
alcuronium	<i>bleomycin</i>
allopurinol	bupivacaine
aluminium diacetate	caffeine citrate
aluminium hydroxide	calamine lotion
amidotrizoate	<i>calcium folinate</i>
<i>amikacin</i>	calcium gluconate
amiloride	<i>capreomycin</i>
amitriptyline	carbamazepine
amlodipine	carbidopa
amodiaquine	cefazolin
amoxicillin	cefixime
amoxicillin + clavulanic acid	<i>ceftazidime</i>
<i>amphotericin</i>	<i>ceftriaxone</i>
Bamipicillin	charcoal, activated
anti D immunoglobulin (human)	<i>chlorambucil</i>
antitetanus immunoglobulin (human)	chloramphenicol
antivenom immunoglobulin	chlorhexidine
artemetherartemether + lumefantrine	chlorine base compound
artesunate	chloroquine
ascorbic acid	chloroxylenol
<i>asparaginase</i>	chlorphenamine
atenolol	chlorpromazine
<i>azathioprine</i>	cholera vaccine
azithromycin	<i>ciclosporincilastatin</i>
bacitracin	ciprofloxacin
barium sulfate	<i>cisplatin</i>
BCG vaccine	clavulanic acid
beclometasone	<i>clindamycin</i>
benzathine	clofazimine
benzyl penicillin	<i>clomifene</i>
benznidazole	clomipramine
benzoic acid	clotrimazole

cloxacillin	fluorouracil
coal tar	fluoxetine
codeine	fluphenazine
condoms	folic acid
copper containing device	furosemide
cyclophosphamide	gentamicin
cycloserine	glibenclamide
cytarabine	glucose with sodium chloride glutaral
carbazine dactinomycin	glyceryl trinitrate
dapsone	griseofulvin
daunorubicin	<i>Hemophilus influenzae</i> type b vaccine
deferoxamine	Haloperidol
dexamethasone	Halothane
dextran 70	heparin sodium
diaphragms	hepatitis A vaccine
diazepamdidanosine (ddI)	hepatitis B vaccine
diethylcarbamazine	human normal immunoglobulin
digoxindiloxanidedimercaprol	hydralazine
diphtheria antitoxin	hydrochlorothiazide
diphtheria vaccine	hydrocortisone
dithranol DLmethionine	hydroxocobalamin
dopamine	ibuprofen
doxorubicin	<i>imipenem + cilastatin</i>
doxycycline	immunoglobulin
efavirenz	indinavir (IDV)
efavirenz (EFV or EFZ)	influenza vaccine
efavirenz + emtricitabine + tenofovir	insulin injection (soluble)
eflornithine	intermediate acting
emtricitabine	insulin
emtricitabine (FTC)	<i>intraperitoneal dialysis solution</i>
emtricitabine + tenofoviranalapril	(of appropriate composition)
<i>ephedrine</i>	iodine
epinephrine (adrenaline)	iohexol
ergocalciferol	ipratropium bromide
ergometrine	isoniazid
erythromycin	isoniazid + ethambutol
estradiol cypionate	isosorbide dinitrate
ethambutol	ivermectin
ethanol	Japanese encephalitis vaccine
ethinyl estradiol	<i>Kanamycin</i>
ethinylestradiol + levonorgestrel	Ketamine
ethinylestradiol + norethisterone	lamivudine
<i>ethionamide</i>	lamivudine (3TC)
<i>ethosuximide</i>	levamisole
<i>etoposide factor IX complex (coagulation factors, II, VII, IX, X)</i>	levodopalevodopa + carbidopa
<i>concentrate factor VIII</i>	levonorgestrel
<i>concentrate ferrous salt</i>	levonorgestrel releasing implant
ferrous salt + folic acid	levothyroxinelidocaine
fluconazole	lidocaine + epinephrine (adrenaline)
<i>flucytosine</i>	lithium carbonate
fluorescein	lopinavir
	lopinavir + ritonavir (LPV/r)

lumefantrine
 magnesium hydroxide
 magnesium sulfate
 mannitol
 measles vaccine
 mebendazole
 medroxyprogesterone acetate
 medroxyprogesterone acetate + estradiol cypionate
 mefloquine
 meglumine antimonate
meglumine iotroxate
 melarsoprol
 meningococcal
 meningitis vaccine
mercaptopurine
 metformin
methadone
methotrexate
 methyl dopa
 methyl rosanilinium chloride (gentian violet)
 methylthioninium chloride (methylene blue)
 metoclopramide
 metronidazole
 miconazole
mifepristone
misoprostol
 morphine
 mumps vaccine
 naloxone
 nelfinavir (NFV)
 neomycin sulfate
 neomycin sulfate + bacitracin
 neostigmine
 nevirapine
 nevirapine (NVP)
 niclosamide
 nicotinamide
 nifedipine
 nifurtimox
 nitrofurantoin
 nitrous oxidenorethisterone
 norethisterone enantate
 nystatin
ofloxacin
 oral rehydration salts
oxamniquine
 oxygen
 oxytocin
p-aminosalicylic acid
 paracetamol
 paromomycin
penicillamine

pentamidine
 permethrin
 pertussis vaccine
 phenobarbital
 phenoxymethyl
 penicillin
 phenytoin
 phytomenadione
 pilocarpine
 pneumococcal vaccine
 podophyllum resin
 poliomyelitis vaccine
 polyvidone iodine
 potassium chloride
 potassium ferric hexacyanoferrate (II)
 2H₂O (Prussian blue)
potassium iodide
 potassium permanganate
 praziquantel
 prednisolone
 primaquine
procainamide
 procaine benzylpenicillin
procarbazine
 proguanil
 promethazine
 propranolol
 propylthiouracil
 protamine sulfate
 pyrantel
 pyrazinamide
pyridostigmine
 pyridoxine
 pyrimethamine
quinidine
 quinerabies immunoglobulin
 rabies vaccine
 ranitidine
 retinol
 ribavirin
 riboflavin
 rifampicin
 rifampicin + isoniazid
 rifampicin + isoniazid + ethambutol
 rifampicin + isoniazid + pyrazinamide
 rifampicin + isoniazid + pyrazinamide +
 ethambutol
 ritonavir
 rotavirus vaccine
 rubella vaccine
 salbutamol
 salicylic acid

saquinavir (SQV)
selenium sulfide
senna silver
sulfadiazine
simvastatin
sodium calcium edentate
sodium chloride
sodium fluoride
sodium hydrogen carbonate
sodium lactate
sodium nitrite
sodium nitroprusside
sodium thiosulfate
sodium valproate
spectinomycin
spironolactone
stavudine (d4T)
stavudine + lamivudine + nevirapine
streptokinase
streptomycin
sulfadiazine
sulfadoxine
sulfadoxine + pyrimethamine
sulfamethoxazole
sulfamethoxazole + trimethoprim
sulfasalazine
suramin sodium
suxamethonium
tamoxifen

tenofovir
tenofovir disoproxil fumarate
testosterone
tetanus vaccine
tetracaine
tetracycline
thiamine
thiopental
timolol
triclabendazole
trimethoprim
tropicamide
tuberculin, purified protein derivative (PPD)
typhoid vaccine
urea
valproic acid
vancomycin
varicella vaccine
vecuronium
verapamil
vinblastinevincristine
warfarin
water for injection
yellow fever vaccine
zidovudine
zidovudine (ZDV or AZT)
zidovudine + lamivudine + lamivudine
+ nevirapine + zinc sulfate

Glossary

Medical, dental and pharmacological terms are included here which are not defined in all chapters but which may be of value in improving the reader's understanding of a topic.

Achlorhydria Absence of hydrochloric acid from the gastric juice.

Acidosis A condition in which the acid/base balance of body fluids is disturbed, thereby decreasing the alkaline content or increasing the acid concentration.

Adsorbent A substance that can adsorb (suck) other substances to its surface without any chemical reaction.

Adulterated Impurity added.

Agranulocytosis A great reduction of certain white blood cells, the polymorphonuclear leukocytes (PMNLs), basophils, and eosinophils.

Albuminuria protein (albumin) in the urine.

Alkaloid A basic chemical contained in many drugs that is made from plants or manufactured synthetically.

Alopecia Hair loss.

Amblyopia Defective eyesight without any apparent defect of the eye. The condition may be temporary or permanent and it may be partial or result in total blindness in the affected eye. It may be caused by poisons like tobacco, alcohol, lead arsenic etc.

Amenorrhea The absence or sudden cessation of the menstrual blood flow.

Anaerobe A microorganism that grows only when there is little or no oxygen present.

Analgesia Relief of pain.

Angina pectoris A severe, paroxysmal pain in the chest accompanied by a feeling of oppression or suffocation due to an insufficient supply of blood oxygen to the heart muscle. These symptoms are usually precipitated by exertion or excitement.

Angioedema Swelling of body tissues with bronchoconstriction, usually as part of an allergic reaction.

Anomaly An abnormality or defect of a body organ or structure.

Anorectal Referring to the lowest portion of the intestinal tract, the anal canal and the rectum.

Anoxia Absence of oxygen in blood or tissues.

Antacid An alkaline drug that neutralizes excessive stomach acids.

Antibody A chemical compound produced by the body to combine with and neutralize a particular foreign substance, called an antigen. Entering the body.

Anticoagulant A drug given to inhibit/slow the clotting or coagulation of the blood.

Antidote An agent or substance that counteracts a poison applied to the body externally or via ingestion.

Antiemetic An agent or substance that counteracts nausea and/or vomiting.

Anti-flatulent An agent or substance that counteracts excessive gas in the intestinal tract.

Antigen Any substance the immune system identifies as a potential threat that starts the reaction leading to the production of a special antibody.

Antimicrobial (antibacterial) An agent that acts to destroy or inhibit the actions of disease-causing microorganisms such as bacteria.

Antipruritic An agent that decreases, stops, or prevents itching.

Antipyretic An agent that reduces fever.

Antiseptic An agent that inhibits the growth and development of microorganisms, such as bacteria.

Antisialagogue Inhibiting saliva flow.

Antitoxin An agent that neutralizes a specific toxin that is released by bacteria.

Aphasia The inability to speak, write, or communicate via appropriate signs, or to understand the writing or speaking of others, usually as a result of brain damage.

Aphrodisiac Increasing sexual desire.

Apnea Absence of breathing.

Aromatic A medicinal substance with a spicy odor and sometimes stimulant properties.

Arrhythmia A variation from a normal rhythm; usually refers to abnormal heart activity.

Arteritis Inflammation of one or more arteries.

Arthralgia Pain in a joint.

Ascites An abnormal collection of fluid in the abdominal area due to disease conditions of one or more organs such as the liver, the heart, or the kidneys.

Aspirate Fluid or tissue removed from the body via suction.

Asthma A breathing disorder caused by infection or allergy in the bronchi.

Ataractic A tranquilizer.

Ataxia Loss of muscle coordination.

Atelectasis Collapse of a portion of a lung.

Atrophy The wasting of tissue, muscles, or any other body part or organ.

Auscultation The act of listening to various sounds, such as those produced by the heart or the lungs, with the ear or with a stethoscope.

Autoantibody An antibody produced by the body in reaction to its own tissues.

Auto-antigen A substance present in the body to which an individual is allergic.

Autogenous vaccine A vaccine prepared from material taken from the body of a person who will subsequently receive the vaccine.

Autoimmune disease A condition caused when the body produces antibodies against its own tissues.

Autosomal inheritance Inherited traits passed on by genes located in 22 pairs of autosomes, which carry all characteristics other than those of sex.

Avitaminosis A deficiency of essential vitamins.

Azotemia Presence of urea or similar substances in blood.

Bacillary Referring to a bacillus, a rod shaped type of microorganism occurring in some forms that are harmless, and in others that cause disease.

Bacteremia Presence of bacteria in the blood.

Bactericidal Lethal to bacteria.

Bacteriostatic Inhibiting growth or multiplication of bacteria.

Basophil A white blood cell with a bent lobe nucleus that is coarsely granular and stains with basic dyes; capable of releasing substances such as histamine and heparin; granular leukocyte; granulocyte

Biliary Referring to the gallbladder or any portion of the gallbladder tract.

Blepharitis An inflammation of the eyelids.

Blood-brain barrier A mechanism (anatomical barrier) that prevents many substances that circulate in the blood, such as certain drugs, from getting into the circulation of the brain.

Blood gases Gases, such as oxygen and carbon dioxide that are dissolved in the blood.

Blood pressure The pressure exerted by the circulating blood against the walls of the blood vessels through which it flows.

Blood volume The amount (volume) of blood in the body at any time, generally considered normal at 8 to 9 percent of body weight.

Bone marrow Tissues that are contained in the cavities of bones. Red bone marrow contains developing red blood cells, white blood cells and platelets, while yellow bone marrow consists of a fatty substance.

Bowel incontinence Inability to retain or control bowel movements.

Bronchitis Inflammation of the lining of the bronchi or air passage of the lung.

Bronchopneumonia Inflammation, usually due to infection, of the lower portions of the bronchi (bronchioles) and the lungs.

Bronchoscopy Visualization of the windpipe (trachea) and the bronchial structures via an endoscope (a lighted instrument passed into these areas) for examination or treatment.

Bruxism Clenching or grinding of the teeth, usually done during sleep.

Bulla A large blister or vesicle filled with serous fluid.

Bursitis Inflammation of a bursa, a saclike cavity filled with a thick fluid that lubricates areas otherwise likely to sustain damage through friction; mainly affects bursae near joints, or those underneath the tendons that move the joints.

Carciferol (vitamin D) An essential nutritional substance that affects the development of bone. Insufficient intake of this vitamin may cause bone disease.

Callus A hardened portion of skin, usually found on the palms of the hands or the soles, due to continual pressure and friction on these areas.

Calorie A unit of heat content or energy.

Candidiasis A fungal infection of the mouth, skin, intestine or vagina caused by *Candida albicans*.

Canker sore A small, usually ulcerated sore on the lips or lining of the mouth, due to fever, irritation, or vitamin deficiency.

Capillary A tiny blood or lymph vessel.

Carcinogen Any substance in the environment or in food, or in some other agent that may contribute to the development of cancer.

Cardiac arrest A sudden cessation of the pumping of the heart that is fatal if not reversed within a few minutes.

Cariogenic That which promotes dental caries.

Cardiovascular Relating to the heart or to the blood vessels.

Cartilage Whitish, tough, flexible tissue situated around joints, in the spinal column, the ears, windpipe, voice box (larynx) and the tip of the nose.

Catabolism The breakdown process of food during digestion into less complex substances.

Cataract A condition in which the lens of the eye becomes cloudy, impairing vision. This process may be due to aging, disease, trauma, or may sometimes be found at birth as a congenital condition.

Cathartic A drug that speeds up the emptying action of the bowel.

Catheterization A process in which a tube is passed into a body organ to empty it, as in urinary catheterization, or for diagnostic or treatment purposes.

Cellulitis Inflammation of cellular or connective tissue in various parts of the body.

Cerebral hemorrhage Bleeding from an artery or other blood vessel in the brain, caused by weakness, injury, congenital abnormality or a disease such as high blood pressure.

Cerumenolytics Agents or drugs that dissolve ear wax.

Chancere A symptom of syphilis, a venereal disease caused by spirochete bacteria called *treponema pallidum*. The chancre is a hard skin lesion that occurs during the first stage of the disease, at the site where the spirochetes entered the body.

Chemotherapy Treatment of disease with the use of chemicals or drugs.

Chilblains The swelling, reddening, and itching of body parts such as the hands, fingers, nose and ears following prolonged exposure to cold.

Chloasma Brown pigmented spots or patches on the skin of the face and other parts of the body that occur with pregnancy, the menopause, or with the use of oral contraceptives.

Cholecystitis Inflammation of the gallbladder.

Cholestatic jaundice Condition characterized by yellowness of skin, whites of eyes, mucous membranes, body fluids, resulting from deposition of bile pigment and excessive bilirubin (hyperbilirubinemia) owing to obstruction of bile.

Cholesterol A component of animal fat, blood, nerve tissue, and bile, some of which is necessary to a healthy body, but that may be harmful in excess, as in the formation of atherosclerosis.

Chorea Twitching, involuntary and irregular movement of the muscles that occurs in a number of nervous system diseases.

Chronotropic Affecting the heart rate.

Cirrhosis A degenerative disease of the liver in which liver cells are destroyed and replaced by useless fatty or fibrous tissue.

Clonic Contraction of muscles alternating with relaxation.

Coagulation The clotting of blood.

Cobalamin (Vitamin B₁₂) An essential nutritive substance required for the adequate development of the red blood cells, for normal functions of the nervous system, and for various other cellular functions.

Colchicine Alkaloid obtained from colchicum (meadow saffron); used in treatment of gout.

Colic Abdominal pain usually caused by cramps in the intestine or stomach.

Colitis Inflammation of the lower portion of the bowel (colon).

Collagen The predominant protein of the white fibers in connective tissue, cartilage, and bone.

Colonoscopy The visualization of the inside of the colon with a lighted tube called a colonoscope that is passed into the colon through the rectum.

Colostomy An opening into the colon, created by abdominal surgery, to relieve an intestinal obstruction or other disease of the colon. This allows the discharge of feces through the opening instead of through the rectum.

Coma A level of unconsciousness from which a person cannot be aroused. Coma may be due to disease, drug abuse, other forms of poisoning, or injury.

Complete blood count A laboratory examination done to determine whether a person has the normal quantity and appearance of blood constituents.

Congener One of two or more things of the same kind.

Congenital A condition, deformity, or disease present at the time of birth.

Congestive heart failure A condition in which the heart fails to provide sufficient pumping action to circulate blood adequately, resulting in congestion of the lungs and other vital organs due to the accumulation of blood.

Conjunctivitis Inflammation of the mucous membrane that lines the eyeballs and the inner parts of the eyelids.

Contact dermatitis An inflammation of the skin caused by direct contact with an irritant.

Contusion A bruise; the swelling and discoloration that appear on the skin after an injury that does not break the skin.

Convulsion Seizure; the contraction of muscles in the entire body, or a body part, with resulting contortion of the

affected parts. This condition may occur due to disturbances of the nervous system, as a symptom of epilepsy, during periods when an individual has a very high temperature, and in various other disease states.

Cornea The clear, transparent portion of the eye that permits the entry of light, refracts light rays and helps focus the eye.

Coryza Nasal discharge and inflammation of the upper respiratory tract, as occurs during a cold, or in persons who have hay fever.

Counterirritant A substance or medication applied to the skin to irritate and mildly inflame it, in order to produce a feeling of warmth and comfort; helpful when applied to painful muscle areas.

Covalent bonds A chemical bond of atoms formed by the sharing of an electron and found in most organic compounds.

Cranium The bony structure of the skull that contains the brain.

Cushing's syndrome Group of symptoms produced by an excess of adrenocorticosteroid.

Cyanosis A bluish or purplish discoloration of the skin and mucous membrane due to poor circulation or a lack of oxygen in the blood.

Cycloplegia Paralysis of accommodation; loss of power of ciliary muscle of eye.

Cyst A sac of tissue anywhere in the body that contains fluid, gas, fatty or other matter.

Cystitis Inflammation of the urinary bladder, usually due to irritation or infection.

Cystoscopy Examination of the urinary bladder and the lower portion of the urinary tract with a lighted instrument called a cystoscope.

Cytotoxic Any substance, drug, or other matter that is harmful to cells.

Decongestant A drug that relieves the discomfort and inflammation (congestion) caused due to cough cold, by shrinking the mucous membranes of the nose.

Decubitus (bed sore) A condition caused by being bedfast, disabled, or having to lie in one position for a long time, allowing pressure on the area to break down the skin and the underlying structures. It can be prevented by frequent change of position, exercise, good skin care and good nutrition.

Dehydration Great loss of body fluid due to vomiting, diarrhea, loss of blood and other disease conditions.

Delirium A condition of confusion and restlessness, due to psychological or other causes, such as high fever.

Delirium tremens Also known as the DT's; a condition of confusion and disorientation commonly associated with chronic alcoholism.

Delusion A psychological disturbance in which a person has a false impression, belief, or concept which he is convinced is true; reasonable discussion or argument will not change his belief.

Dementia Impairment of the mind caused by injury or disease; generally appears together with emotional and behavioral disturbances.

Demulcent A substance or drug that soothes and relieves irritations of such body surfaces as the skin and mucous membranes.

Dermatitis Any inflammation of the skin. This condition is caused by infection, irritation, or other disease.

Dermatologic Referring to skin, or the treatment of a skin condition.

Desquamation Loss of epithelium.

Diabetes insipidus A condition characterized by only polyuria without hyperglycemia and glycosuria.

Diabetes mellitus It is a metabolic disorder characterized by polyuria, polyphagia and polydipsia, where carbohydrate metabolism is reduced while that of protein and lipid are increased. Therefore associate with hyperglycemia and glycosuria.

Diaphoresis Perspiration or sweat that is visible or perceptible.

Diaphoretic A substance, drug, or measure used to increase sweating.

Diastolic phase of blood pressure (diastole) The lowest level noted during blood pressure measurement. It reflects the pressure within the artery and the heart's chambers as the heart muscles relax and the chambers fill with blood to prepare for the next contraction.

Diplopia Double vision.

Disorientation A mental state in which a person is confused, may not recognize other persons, know the time or place, or other facts, This state may be due to a disease process or to toxic states such as alcohol or drug abuse.

Diuretic A substance or drug that causes increased urination.

Divalent Has an electrical combining charge of two units, such as Ca^{++} .

Dorsal horn neurons Neurons in the dorsal (back) region of the spinal chord that transmit sensory information to the brain.

Dosage The exact quantity of a drug that has been prescribed for a given time period.

Duodenal ulcer A lesion in the duodenum that results in the loss of tissue due to inflammation. The ulcer may penetrate the wall of the duodenum causing hemorrhage and other complications. It is caused by excessive secretion of stomach acid, intake of certain drugs, foods, or stress.

Dwarfism A condition in which a person remains abnormally small.

Dysentery An inflammation of the colon characterized by pain, cramps and diarrhea caused by bacterial, viral or amebic infestation.

Dysmenorrhea Pain during menstrual periods.

Dyspepsia Upset stomach or indigestion.

Dysphagia Difficulty in swallowing.

Dysphasia Difficulty in speaking, and in expressing oneself understandably to others, usually due to brain damage.

Dysphoria Unpleasant feelings.

Dyspnea Difficulty in breathing; shortness of breath, usually due to disease of the heart or lungs.

Dystrophy, muscular A disease of unknown origin in which muscles do not function normally, and eventually deteriorate.

Dysuria Difficulty or pain during urination.

Ecchymosis An area of purplish discoloration on the skin, due to bleeding underneath that area.

Eclampsia A condition in which a pregnant woman develops convulsions (seizures) shortly before, or during labor, as a result of having high blood pressure during the pregnancy associated with kidney problems.

Eczematous An acute or chronic inflammatory condition of the skin, due to allergy or other causes.

Edema Swelling in body tissues or in a body part caused by the accumulation of fluid.

Edentulous Toothless.

Electrocardiogram (ECG) A record made by a machine called the electrocardiograph that traces the electrical activity of the heart, and indicates abnormalities if any are present.

Electroencephalogram (EEG) A record made by a machine called an electroencephalograph that traces the electrical activity of the brain (brain waves).

Electromyogram (EMG) A record made with a machine called an electromyograph that traces the electrical activity of muscles. It is used to diagnose muscle diseases.

Embolism An obstruction in a blood vessel by a traveling blood clot or various other substances.

Emetic A drug used to induce vomiting.

Emollient A substance or drug that smoothes and softens irritated skin or mucous membranes.

Emphysema A condition in which the lungs have enlarged air sacs which cause difficulty in breathing.

Empyema The formation of pus in one of the body cavities, frequently the lung.

Endometriosis A condition in which cells that normally line the walls of the womb begin to grow on the surfaces of other organs within the pelvic structure, and sometimes also in distant areas of the body.

Endometrium The mucous membrane that lines the womb (uterus).

Endotoxin A toxic (poisonous) substance released by certain microorganisms inside the body when their cell walls are destroyed (lyses).

Enteric Related to intestines.

Enteritis Inflammation of the intestinal tract.

Enterocolitis Inflammation of the small and large intestines.

Enterovirus A virus that lives in the intestinal tract.

Eosinophilia Increase in the number of eosinophils, one of the white blood cell types.

Epidemic A contagious disease that spreads through a large area of a community, a country, and sometimes an entire continent.

Epidermis The outermost portion of the skin.

Epiglottis A piece of cartilage behind and below the tongue that closes the top of the windpipe (trachea) when a person is about to swallow, so that the food will go down the gullet (esophagus) and not the windpipe.

Epilepsy A disease of the nervous system in which the victim has convulsions (seizures) and lapses of unconsciousness at different intervals.

Epiphysis The end portion of long bone.

Epistaxis Bleeding from nose.

Eructation The act of belching.

Erysipelas A painful infection of the skin caused by streptococcus bacteria.

Erythema A reddened condition of the skin, due to irritation or infection.

Erythroblast Any form of human red blood cell that contains a nucleus.

Erythrocyte sedimentation rate (ESR) A laboratory test that determines the presence of infection in the body.

Esophageal Referring to the esophagus (gullet).

Esophagoscopy Examination of the inside of the esophagus (gullet) with a lighted tube called an endoscope.

Etiology The study of the causes of diseases.

Euphoria A feeling of excessive abnormal happiness and well-being, not necessarily based on reality, that may be caused by a drug or illness.

Exfoliative dermatitis Inflammation of the skin with scaling-off of dead skin.

Exocrine A glandular secretion delivered directly, or through a duct to the linings of body parts or to the skin.

Exogenous Having an outside source.

Exophthalmos A condition in which the eyeballs protrude; present in certain diseases.

Expectorant A medication that helps in getting rid of mucus and phlegm that has accumulated in the respiratory tract.

Extrapyramidal Brain structures affecting body movement; a term used to describe adverse drug effects that result in body movement.

Extravascular Occurring outside a blood or lymphatic vessel.

Fibrin A body protein essential in the clotting of blood when blood is exposed to air, such as during an injury.

Fibrosis Scar tissue that is formed after injury or surgery.

Fibrositis An inflammation of fibrous tissue.

Fistula A passage or channel that is formed between two internal body parts, or between an interior part of the body and the surface.

Fluorosis Tooth discoloration due to high amounts of fluoride during tooth formation.

Folacin (folic acid) An essential nutritive substance required for the proper development of red blood cells. Deficiency causes various forms of anemia.

Foreign body Any substance or material embedded in a part of the body where it doesn't belong and where it may cause injury.

Furuncle A boil; an infected area of skin filled with pus.

Ganglion, ganglia Group of nerve cell bodies.

Gangrene Death of body tissue. It is usually caused by a reduction or complete absence of blood to a section of tissue. It may be result of burns, freezing, physical injury, a blood clot and bacterial or any other infection.

Gastric lavage A process of washing out the stomach, needed when a toxic substance has been ingested that must be removed as part of the treatment that helps the victim to survive.

Gastritis Inflammation of the stomach.

Gastroenteritis Inflammation of mucous membrane of the stomach and intestine.

Gastrointestinal Refers to the stomach and the intestines.

Genitourinary Refers to the genital and urinary tract areas.

Geriatric Refers to the elderly.

Germicide Any substance or drug that can kill germs.

Gestation The period of development of a child from the time of fertilization of the ovum to birth.

Gigantism A condition in which a person has an unusually large body, or body parts.

Glaucoma An ophthalmic condition in which the intraocular pressure within the eye rises, with or without accompanying pain. If the condition is not recognized, damage to eye structures and loss of vision may result.

Glossitis Inflammation of the tongue.

Glucagon A body hormone that activates sugar stored in the liver; it also affects various other body functions.

Glucose Body sugar (carbohydrate).

Glycogen The form in which glucose is stored in the liver.

Glyconeogenesis (Gluconeogenesis) Formation of carbohydrates from non-carbohydrate sources such as protein and fat.

Glycosemia The presence of sugar in the blood.

Glycosuria Urinary excretion of carbohydrates.

Gout A disease due to an unusually high amount of uric acid in the blood. Uric acid is deposited in the tissues, since the kidneys can't excrete the increased amount rapidly enough. Gout affects joints such as the big toe, which becomes inflamed, hot and painful.

Granulocyte A white blood cell.

Granulocytopenia Less than the normal number of granulocytes in the blood.

Granuloma A nodular inflammatory lesion that contains areas of granulation. When found around the groin and genitals it is generally granuloma inguinal, a venereal disease that requires specific medical treatment.

Hallucinogen A substance or drug that produces unrealistic perceptions in the individual who takes it.

Hematemesis Vomiting blood.

Hematinic An agent or drug that increases the number of red blood cells in the blood, as well as the concentration of hemoglobin.

Hematologic Referring to blood, or the study of blood.

Hemotoma A collection of blood, or of clotted blood somewhere in the body, usually caused by injury or following surgery.

Hematopoiesis Process of formation and development of various types of blood cells.

Hematuria Blood in the urine.

Hemiplegia Paralysis of one side of the body, frequently due to a stroke.

Hemolysis Destruction of red blood cells; occurs in infection, due to a toxic substance or drug, or in the laboratory after freezing, thawing, or other activities or studies involving red blood cells.

Hemophilia An inherited disorder in which the affected individual bleeds easily and may develop serious hemorrhage even after very minor injury, due to the presence of a clotting factor deficiency.

Hepatitis Inflammation of the liver, usually due to infection, or following ingestion of a toxic substance.

Hepatosplenomegaly Enlargement of the liver and spleen.

Hernia A condition in which an organ inside one of the body's cavities protrudes from the cavity, usually due to a weakness of the muscles that surround it, or following disease or surgery.

Hiatal hernia Portion of stomach extruding through diaphragm into chest cavity.

Hirsutism A condition characterized by the growth of hair in unusual places and/or excessive amounts, especially in women.

Homologous That which has the same relative position, value, or structure.

Humectant An agent or substance that helps to preserve moisture in specific body areas such as the skin; or in room, or in an oxygen tent.

Hydrocephalus A condition which may be congenital or acquired, in which the head becomes abnormally large, and there is increased pressure in the brain, due to excessive secretion and accumulation of cerebrospinal fluid in the ventricles (chambers in the brain).

Hydrogen bond A chemical bond occurring when a hydrogen atom joins two other atoms.

Hyperglycemia An excessive amount of sugar in the blood; occurs in uncontrolled diabetes mellitus.

Hyperkalemia Excessive amount of potassium present in the blood.

Hyperplasia An increase in tissue or size of an organ due to cell multiplication.

Hyperpnea Abnormally rapid and deep breathing.

Hyperpyrexia Excessively high fever.

Hyperthyroidism Increased secretion of thyroid hormone from the thyroid gland.

Hypertrophic Excessive growth of an organ or body part by cell enlargement.

Hyperuricemia Increased uric acid in blood.

Hyperventilation Abnormal increase in the depth and/or rate of breathing that may cause dizziness and occasional fainting.

Hypnotic An agent or drug given to induce sleep.

Hypocalcemia An insufficient amount of calcium in the blood.

Hypochondria Abnormal preoccupation with one's health.

Hypogeusia Loss of sense of taste.

Hypoglycemia An abnormal lack of sugar (glucose) in the blood.

Hypokalemia Insufficient amount of potassium in the blood.

Hypoprothrombinemia Abnormally small amounts of prothrombin in the blood.

Hyposmia Loss of sense of smell.

Hypotension Abnormally low blood pressure.

Hypothermia Abnormally low body temperature due to accidental exposure to cold, immersion in cold water, or intentionally induced as a treatment or during surgery by using an electrically controlled hypothermia mattress.

Hypothyroidism Decreased secretion of thyroid hormone from the thyroid gland.

Hypoventilation Reduced ventilation.

Hypovolemic shock A state of shock caused by a greatly reduced volume of blood, generally due to hemorrhage.

Hypoxemia Inadequate oxygenation of blood.

Hypoxia A condition caused by a lack of oxygen in the body.

Idiopathic thrombocytopenic purpura (ITP) A blood disease of unknown origin whose chief symptom is platelet destruction, which leaves the victim prone to bleed.

Idiosyncrasy (to drugs) Unusual response to certain drugs by some individuals.

Ileostomy An opening created by surgery in the abdomen and the ileum (section of small intestine) to allow discharge of fecal material.

Immunization, active It is the administration of antigen to the host in order to induce antibody production. Vaccines are used for active immunization.

Immunization, passive It is imparting immunity to a host passively by the transfer of antibodies, e.g. antisera and immunoglobulins (Ig). This affords immediate protection, as readymade antibodies are available.

Immunoglobulins Body proteins (like gamma globulins) that function as antibodies to ward off infection.

Immunosuppression Suppression of the body's defensive (immune) mechanism by means of certain drugs.

Immunotherapy Treating the body in such a way as to bolster (enhance) its capacity to ward off infection or the invasion of harmful foreign cells such as cancer cells.

Infection The presence of an organism, such as bacteria or virus or any microorganism that can have a harmful effect on the body.

Inflammation Redness and swelling, accompanied by heat and pain.

Influenza A contagious viral infection of the upper respiratory tract.

Inguinal hernia Protrusion of a portion of intestine through a weakened muscular wall in the groin (inguinal region).

Insulin A hormone produced by cell groups inside the pancreas (a gland lying across and behind the stomach) called the islets of Langerhans. Insulin converts blood sugar into body energy.

Insulinoma A tumor (growth) of the cell groups called islets of Langerhans in the pancreas, which may produce excessive amounts of insulin.

Interferon A natural body substance formed in response to infection that defends the body against further attack by the foreign cells, organisms, or viruses.

Internist A physician who specializes in the diagnosis and non-surgical treatment of disease.

Interstitial Relating to a space between cells or inside a body organ.

Intra-articular Inside a joint.

Intramuscular Into muscular tissue.

Intubation Insertion of a tube into a body opening or passage.

Irritant A drug or agent that irritates the skin or other body part, either accidentally or with intent to produce tissue stimulation.

Ischemia A deficiency of blood in an organ or part of the body. Ischemia is caused by obstruction of the blood vessels that supply an organ or area of the body. Such obstruction may be the result of narrowing, compression or damage from condition such as a blood clot or atherosclerosis and causes oxygen loss that leads to tissue death in the affected area.

Jaundice A condition caused by bile pigments in the blood, manifested by a yellowing of the skin and other tissue, and caused by disease or other abnormality, often a disease causing the yellowing of the skin is itself called a jaundice.

Keratitis Inflammation of the cornea, the transparent structure located at the front of the eye.

Koplik's spots Tiny blue and white spots surrounded by red rings that appear inside the mouth at the points where the upper and lower teeth meet. The spots appear during the first two or three days of the onset of measles, before the rash can be seen.

Kwashiorkor A condition of extreme malnutrition, especially of proteins. Occurs in children who live in poor countries, or in areas of deprivation. They develop anemia, swelling of body tissues, a pot belly, and other physical characteristics.

Labyrinthitis Inflammation of the structures of the inner ear.

Lacrimal apparatus The tear glands, sacs, and ducts that produce tears, and carry them down through the eyes and into the nose.

Lactation The process following childbirth during which milk is formed in the mother's breasts to enable her to nourish her infant through sucking.

Lactic dehydrogenase (LDH) An enzyme in the blood that rises to higher levels within several days after a person has had a heart attack. Laboratory determination of this and other enzymes helps to make a diagnosis of heart attack, and to distinguish this condition from various other diagnoses.

Lactose Milk sugar.

Laryngitis Inflammation of the larynx (voice box).

Laryngospasm Contraction of laryngeal muscles.

Lavage The washing out of an organ or body cavity, such as the stomach (gastric lavage).

Laxative Mild cathartic; remedy that promotes evacuation of the bowel.

Lethargy Condition of sluggishness or lassitude.

Leukemia Also known as cancer of the blood, leukemia is a disease of the blood-forming organs, which produces a large number of abnormal white blood cells. The disease occurs in acute and chronic form.

Leukocyte A white blood cell (WBC).

Leukocytosis Increase in the number of leukocytes in circulating blood.

Leukopenia Less than normal amount of leukocytes (WBC) in circulating blood.

Leukoplakia Small whitish, sometimes leathery patches on the skin or mucous membrane that occur due to various cause. It is considered to be a pre-cancerous lesion.

Lipoma A benign growth composed of fatty tissues.

Lipoproteins Body compounds that contain both proteins and fatty substances.

Lues Syphilis.

Lumbago A general term for backache in the lower part of the spine, mid or lower back, or the lumbar and/or lumbo-sacral area. It also includes rheumatic pain.

Lymphadenitis Inflammation of the lymph nodes, which are located throughout the body along the lymphatic channels.

Lymphadenopathy Abnormal, usually enlarged lymph nodes.

Lymphangitis Inflammation of the lymphatic channels.

Lymphoma A general term applied to a tumor like growth of lymphatic tissue.

Malady Any condition that exhibits symptoms of illness or disease.

Malaise A term that describes a general feeling of illness, headache, muscular, joint, and other pains that occur when a person has the flu or other febrile illness.

Malignant Any condition that is resistant to treatment, is very severe, and may lead to death.

Malocclusion Failure of the upper and lower teeth to meet properly when the mouth is closed.

Mastication Chewing

Mastitis Inflammation of the breast.

Mastoiditis Inflammation of the mastoid, a bone located behind the ear.

Melanoma A tumor that appears on the skin. If malignant, it may spread to other parts of body. The lesion is dark brown due to the pigment melanin.

Melasma (chloasma) A patchy discoloration of the skin, often seen in pregnant women.

Menarche The onset of the first menstrual period.

Meningocele A body defect in which a portion of the spinal cord membrane protrudes through the bones of the spinal column.

Menorrhagia Excessive bleeding during the menstrual period.

Metabolism The sum of all the physical and chemical processes by which living, organized substance is produced and maintained.

Methemoglobinemia Presence of methemoglobin, a poor carrier of oxygen, in the red blood cells; gives the blood a chocolate brown color.

Migraine A severe headache that may appear on only one side of the head and cause other symptoms such as nausea, vomiting, and a special sensitivity to light and noise.

Moniliasis Infection with a species of the fungus *Candida*; formerly candidiasis.

Mucus The material secreted by the mucous membranes.

Myalgia Muscular pain.

Mydriasis Dilation of the pupil.

Myocardial infarction The sudden loss of blood supply to the heart muscle due to a dangerous narrowing of one of the blood vessels such as the coronary artery, or an obstruction such as a blood clot. Commonly called a heart attack.

Myocardium Heart muscle.

Myoclonic Pertaining to alternate contraction and relaxation of muscle or group of muscles.

Myoma Excessive growth of muscular tissue into a tumor.

Myositis Inflammation of a muscle, or a group of muscles.

Narcosis Stpor.

Nacrolepsy A disorder characterized by sudden, uncontrolled lapses into deep but brief sleep.

Nausea A feeling that one wants to vomit.

Necrosis Death of cells, tissues, or organs due to lack of oxygen, infection, injury, exposure to cold or burn.

Neonatal Concerns the newborn period, generally the first four weeks after birth.

Neoplasia A pathologic process that results in the formation and growth of a tumor.

Nephritis Inflammation of the kidneys.

Nephropathy Disease state affecting the kidneys.

Neuralgia Pain that travels along peripheral nerve tracts.

Neuritis Inflammation of one or more nerves.

Neuroma A tumor that arises from cells somewhere in the nervous system.

Neurosis It is a behavioral, emotional or psychological disorder which is associated with many symptoms; the most frequently apparent symptom is anxiety.

Neurotransmitter A chemical released by a nerve that transmits information (action potential) from a nerve to another nerve or to an organ.

Neutropenia A disorder in which the number of white blood cells in the body is decreased.

Nevus A mole or birthmark.

Nocturia Frequent urination during the night due to excessive fluid intake before going to bed at night, or to illness.

Nodule A small swelling.

Nonmyelinated nerves Nerves which are not surrounded by myelin sheath, which is a fat like substance forming a sheath around some nerve fibers.

Nyctalopia Night blindness.

Nystagmus An involuntary, rapid movement of the eyeball.

Occult blood Blood present in such small quantities and often altered in color or consistency that it can be detected only by chemical tests, or via microscopic or spectroscopic examination of the suspected material.

Ointment A semisolid preparation which usually contains a medication.

Oligomenorrhea Abnormally infrequent or scanty menstruation.

Oncology The study of cancerous diseases.

Ophthalmic Refers to the eye.

Opiate A natural substance found in opium such as morphine or codeine and any drug that is chemically related.

Opioid A substance that acts like an opiate but differs in chemical structure.

Orthopedics The branch of medicine that deals with disease and injury of the muscle, bones and joints.

Orthodontia The branch of dentistry that deals with the correcting of irregularities of the teeth.

Orthostatic hypotension Low blood pressure on arising.

Osmosis A process in which fluid flows from one area where the liquid is of a lower concentration across a semi-permeable membrane to an area in which liquid is of a higher concentration.

Ossification The transformation of soft tissue into bone or bone like tumor.

Osteoarthritis A degenerative disease that affects the joints, and often occurs as a person ages or following injury.

Osteoma A benign tumor comprised of bone.

Osteogenic sarcoma A malignant bone tumor that most often occurs in the young between the ages of 10 to 20.

Osteomalacia Softening of the bone. A bone disease in which the bones soften and bend, with varying degrees of pain.

Osteoporosis A decrease in bone density.

Osteosclerosis An increase in bone density.

Otitis media Inflammation of the middle ear.

Otorhinolaryngologic Refers to the ear, nose, and throat.

Oxytocic A drug or agent that speeds up the onset of strong uterine contractions during labor. It may also be given after delivery to cause the uterus to contract and prevent uterine bleeding.

Pacemaker A network of muscle fibers in the right ventricle of the heart that control the rhythm of the heart-beat, an artificial device that stimulates heart action and regularizes the heartbeat by the periodic discharge of electrical impulses.

Pallor Paleness of the skin.

Palpation Using the hands to touch, feel, or lightly press a certain body area to determine if any abnormality is present.

Palpitation A very rapid heart beat caused by exertion (such as running), by excitement, nervousness, certain drugs, and various disease conditions.

Pancytopenia Pronounced reduction in the number of erythrocytes, leukocytes, and platelets in blood.

Paracentesis A puncture of a body cavity for the purpose of removing fluid.

Pardoxical Inconsistent with or opposed to known facts.

Paralysis Inability to move the extremities or a body part due to loss of muscular function.

Paranoid A condition in which a person is abnormally suspicious of others, with feelings of delusion and of being persecuted by hostile people or forces.

Paraplegic A condition in which both legs, and usually the lower portion of the trunk are paralyzed. This may happen after a stroke, an injury to spinal cord, and under certain other circumstances.

Parasite An organism that lives on, and obtains its nourishment from another organism called the host.

Parenteral Administered by some means other than through the intestinal canal (GIT).

Paresthesia A feeling of numbness.

Parkinsonism A progressive degenerative disorder in which there occurs degeneration of dopaminergic nerves in nigrostriatal pathway. It is characterized primarily by tremors, muscle rigidity, and a jerky gait.

Paronychia Inflammation or infection in the tissue surrounding a finger or a toenail.

Parturition Childbirth.

Passive immunity Immunity temporarily conferred against a certain infectious disease by inoculating a person with a substance that contains antibodies against that disease.

Pathogen, pathogenic A disease-causing micro-organism.

Pathologic Refers to disease, or to the study of disease.

Pediatric The branch of medical science that deals with the disease and care of children

Pellagra A disease caused by deficiency of niacin (part of vitamin B complex).

Perfusion The passage of a fluid through cells or vessels of a specific body part.

Periaqueductal gray An area around the aqueduct (narrow passage) between the third and fourth ventricles of the brain involved in endogenous analgesia.

Pericardial Pertaining to the sac (membrane) surrounding the heart.

Pericarditis Inflammation of pericardium.

Periodontics The branch of dentistry that deals with the study and treatment of diseases and disorders of the periodontium that is the gum and tissues surrounding and supporting the teeth.

Peritonitis Inflammation of the peritoneum, the membrane that lines the abdominal cavity.

Periventricular gray An area around the third ventricle of the brain involved in endogenous analgesia.

Pertussis Whooping cough.

Petechiae Minute hemorrhagic spots in the skin.

Petit mal A minor seizure in which the affected person may seem to be absentminded, day-dreaming, or twitching slightly for a few seconds, then return to a normal state.

pH Extent of acidity or alkalinity of a solution or medium.

Phenylketonuria (PKU) An inherited metabolic abnormality in which the affected individual is unable to process a certain constituent of protein foods called phenylalanine. If not recognized and treated, early mental retardation may result. The condition can be diagnosed in a newborn baby's urine or blood, and corrected by providing a diet free of foods containing phenylalanine.

Pheochromocytoma A tumor in the adrenal gland that may cause high blood pressure and related symptoms.

Phlebitis Inflammation of a vein.

Photosensitivity Exaggerated response of the skin to sunlight, sometimes related to drugs.

Pinocytosis Ability of cells to engulf fluids.

pKa A constant which is equal to the pH at which a substance in solution is 50 percent in an ionized state and 50 percent in an unionized state.

Pleural Refers to a thin membrane that covers the lungs and lines the inside of the chest wall.

Pleuricy Inflammation of the pleura.

Pneumoencephalogram (PEG) X-ray studies of the brain following the inflation of air or gas to make these structures visible.

Pneumonia Inflammation of the lungs in which the air sacs in the lungs, the alveoli, fill with fluid and WBC. It is due to infection with microorganisms, i.e. *Mycobacterium pneumoniae*.

Pneumothorax A condition that occurs when air or gas gets into the pleural cavity and exerts pressure on the lung, causing it to collapse. When this happens as a result of trauma or rupture of a lung air sac, breathing problems develop requiring prompt treatment.

Podiatry The science that deals with disease irregularities and injuries of the foot; chiropody.

Poliomyelitis An inflammation of the spinal cord that can cause paralysis; infantile paralysis; polio (viral infection)

Polyp A projecting growth of mucous membrane usually not malignant.

Polyuria Excessive urination.

Porphyria A metabolic defect that involves a group of body pigments called porphyrins. Depending on the type of illness, the affected person may have abdominal pain, the nervous system may be involved, and urine may turn dark brown on standing.

Postpartum Referring to the period that follows childbirth.

Postpradial After a meal.

Postural hypotension Low blood pressure on rising; also called orthostatic hypotension.

Preganglionic fibers Nerve fibers preceding the ganglia.

Proctitis Inflammation of the rectum.

Prostatic hypertrophy Benign enlargement of the prostate.

Prothrombin Chemical substance in the blood that is involved in the clotting process.

Pruritus Itching.

Psychiatric Refers to an abnormal mental or emotional state.

Psychosis Severe emotional disturbance in which a person behaves irrationally, unpredictably, and may harm himself or others.

Puberty The period between the initial appearance of secondary sex characteristics and the completion of their development.

Pulmonary Refers to the lungs.

Purkinje fibers Specialized cardiac fibers which carry nerve conduction from the atria to the ventricles.

Purpura Bleeding into the skin as a result of injury or a blood disorders.

Pus A thick, yellowish liquid produced by inflammation or infection. It consists of fluid (serum) and germ-destroying cells, other microorganisms and dead tissue.

Pyelonephritis Inflammation of the kidneys.

Pyogenic Refers to an agent or organism that causes the formation of pus.

Pyrogen Agent that causes a rise in body temperature.

Pyuria Pus in the urine.

Q fever An infection caused by rickettsial microorganisms that occurs mainly in farmers and in slaughterhouse workers.

Quaternary ammonium compounds, Chemical radical (CR)⁴ N⁺ Systemic drugs with this structure remain in an ionized state and do not readily move through cellular membranes.

Quinsy A sore throat, followed by an abscess in the tissues that surround the tonsils. This condition may occur together with tonsillitis. If the abscess becomes very large, it may need to be opened and drained.

Radionuclide A radioactive substance that is used to perform diagnostic and treatment procedures in the field of nuclear medicine.

Reflex An automatic, involuntary or learned response to a stimulus.

Refraction An examination of the eyes by an eye doctor or an optometrist to determine the presence of near-sightedness, farsightedness, or other vision abnormalities prior to prescribing corrective lenses.

Remission The temporary disappearance of symptoms in chronic disease.

Respiratory arrest The sudden cessation of breathing.

Respiratory tract The organs and passages concerned with breathing: the nose, pharynx, larynx, epiglottis, trachea, and the lungs.

Retina The light-sensitive inner layer of the eye that transmits nerve impulses to the optic nerve.

Retinopathy Non-inflammatory degenerative disease of the retina.

Reye syndrome A virus disease usually found in children that may follow an upper respiratory infection or other virus disease. It is dangerous disease that affects the brain and nervous system, and produces fatty accumulations in various body organs.

Rheumatoid arthritis An inflammatory disease of the joints of the fingers, wrists or feet, but which may also affect other joints. It produces pain and swelling, destroys surrounding cartilage, and decreases motion in the affected joints. Rheumatoid arthritis is a chronic disease that may cripple the affected individual. It may affect children as well as adults.

Roentgen An international units of X-and gamma radiation.

Rubefacient A counterirritant which reddens the skin when applied.

Scabies A skin infection caused by a mite that burrows into the skin.

Scarlatina Also called scarlet fever. A skin disease that is highly contagious, caused by a streptococcal organism; symptoms include fever and a bright red rash over the body, followed later by peeling of the affected skin areas.

Scorbutic Relating to or suffering from scurvy.

Scurvy A disease caused by deficiency of vitamin C; symptoms include a tendency of the gums to bleed, inflammation of the gums, and loose teeth.

Seizure A sudden attack of any kind as by an epileptic fit, heart attack, convulsion or a stroke.

Septic Descriptive of that in which bacteria or other infectious substance is present.

Septicemia The presence of harmful organisms or their toxins in the blood stream.

Serum sickness Reaction that sometimes follows the injection of a foreign serum.

Shock A group of symptoms that occur when a person's circulatory system collapses. This may happen in a severe allergic response, when a person hemorrhages, after major surgery, serious burns, or following trauma.

Sinus A small, hollow channel or passage inside the body that may contain fluid or air.

Status-epilepticus Condition in which one major attacks of epilepsy succeeds another with little or no intermission.

Stenosis The narrowing of a channel, duct, or passage in the body.

Sterile An area that is free of germs.

Stimulant A drug or other substance that increases the activity of a process or organ.

Strabismus An eye condition which makes it impossible for a person to focus both eyes on the same place. Treatment may include eye glasses, exercises, medication, and surgery.

Stroke The sudden disruption of blood supply to an area of the brain; apoplexy. Stroke may cause paralysis of one side of the body if the brain is damaged in an area that controls body movements. It is usually caused by chronic high blood pressure or hardening of the arteries (arteriosclerosis).

Subcutaneous injection An injection that is given under the skin.

Sublingually Under the tongue.

Supine Lying on the back.

Supspension A liquid preparation containing fine particles.

Sustained release dosage A term that indicated that a drug has been manufactured so that tiny portions of each tablet or capsule are released over a period of hours at carefully calculated intervals.

Symptom A characteristic indicator of a disease or infection, either evident to the examiner or a sensation described by the subject, that taken with other indicators, forms the basis for a diagnosis.

Synapse The region of contact between processes of two adjacent nerves.

Syncope Fainting.

Syndrome A group of symptoms that occur together, suggesting the presence of a disorder of illness known to include this group of symptoms.

Synergism Interaction of two drugs which causes a more pronounced effected than when either drug is used alone.

Synovial fluid The fluid found in joints.

Syrup A concentrated solution of a sweetening agent, usually a sugar, which is combined with medicinal agents.

Systemic Relating to the body as a whole.

Systole The contraction or period of contraction of the heart.

Systolic phase of blood pressure (systole) The highest level noted during blood pressure measurement. It reflects the pressure within the artery and the heart's chambers as the heart muscles go into systole (contract), forcing blood to be pumped out of the heart, back into the arterial circulation.

Tachycardia A rapid heart rate.

Tachypnea Very rapid breathing.

Tamponade Compression of a body part as a result of an accumulation of fluid in a surrounding body area.

Tapeworm One of group of long worms that lives in the intestines of man as well as in animals; may grow as long as 30 feet.

Tendinitis Inflammation of a tendon, a tough and strong band of connective tissue that connects muscles to bones.

Teratogen Any agent that may cause a growing fetus to be born with an abnormality.

Tetanus An infectious disease caused by *mycobacterium tetany*, associate with sever muscle contractions including Lockjaw.

Tetany A disorder caused by a calcium deficiency in the blood. Inadequate calcium levels produce irritability of the nerves, muscular cramps or spasms, and sometimes convulsions. There are several possible causes for the disease. Depending on the cause, treatment consists of calcium, vitamin D, or parathyroid hormone.

Thermography A technique for determining variance in temperature with the aid of an infrared camera. This allowing a diagnostician to detect areas of abnormal growth or activity.

Therapeutics The branch of medicine concerned with the treatment of disease.

Thrombocytopenia An abnormally small number of platelets in the blood.

Thrombocytopenic purpura Hemorrhage resulting from a reduced number of circulating blood platelets.

Thromboembolism Venous blocking by a blood clot that has been detached from its site of formation.

Thrombophlebitis An inflammation in the blood vessel wall, usually of the legs, with the concomitant development of a risk of the formation of blood clots.

Thrombosis The presence of a blood clot inside a blood vessel, blocking the vessel.

Thrush A fungal infection most often affecting children, that is characterized by the formation of white patches and ulcers in the mouth and throat.

Thyroidectomy Removal of the thyroid gland.

Tic douloureux A condition that irritates the trigeminal nerve which branches out through the face, causing severe

facial pain. Medication, dental therapy, and neurosurgery can provide relief.

Tinnitus A condition in which a person hears noises or ringing in his ears. May be caused by a problem of certain nerves, by inflammation, and by certain drugs.

Tonic State of continuous action; muscle contraction.

Torticollis Wryneck; a contraction of the muscles on one side of the neck that causes the neck to twist and the head to incline to one side.

Toxicology Refers to the study of poisonous agents and how they affect the body.

Toxin A poisonous substance. It may be a chemical agent, or a harmful substance secreted by a micro-organism.

Tracheotomy An incision made into the windpipe when a person is unable to breathe normally.

Transplant To transfer an organ or tissue; the organ or tissue so transferred. Transplants ranges from those of the cornea of the eyes, to skin grafts to those of organs and tissues many yet in the experimental stage.

Tremor A state or trembling (shaking) of one or more body parts, such as the hands or the head due to illness or weakness.

Tumor Any growth of new tissue that is independent of its surroundings. A tumor may be benign or malignant.

Ulcer Descriptive of an erosion, or open sore; any area of skin or mucous membrane that is lacking its normal protective cover and usually, is inflamed.

Ulcerogenic Causing ulcers.

Ultrasonography A diagnostic technique that utilizes the reflection and transmission of ultrasonic waves to determine abnormality or disease of internal body structures.

Uremia The presence of an abnormally high level of urea and other nitrogenous waste substances in the blood, caused by poorly or nonfunctioning kidneys.

Uricosuric Promoting excretion of uric acid and decreasing plasma uric acid concentration.

Urolithiasis The presence of a stone in the urinary tract.

Urologic Refers to the urinary tract.

Urticaria A skin rash which is often associated with severe itching (allergic condition).

Vaccine A preparation that contains infectious organisms that are alive, or that have been inactivated or killed. When given to an individual in carefully prescribed amounts, the system is challenged to develop antibodies against these microorganisms and the disease they cause, so that the individual develops immunity against it.

van der Waals forces Weak intermolecular forces which hold molecules together.

Varices Varicose veins; a condition in which certain veins become dilated, knotted and weakened due to stress or disease (usually in legs).

Vascular Referring to the circulatory system (vessels).

Vascular fragility A tendency of blood vessels to disintegrate due to brittleness, weakness, infection, or disease.

Vasoconstrictor An agent or drug that causes blood vessels to constrict or narrow.

Vasodilator An agent or drug that dilates blood vessels.

Venereal Refers to a disease, infection, or other event affecting the genital area.

Ventricle One of the two lower chambers of the heart. The left ventricle pumps oxygenated blood through the body to nourish the tissues; the right ventricle pumps blood to the lungs to be reoxygenated.

Vertigo Severe dizziness.

Vesicle A bladder or bladder-like structure, as in the case of a blister or sac-like cavity; caused by friction, inflammation, or infection.

Vestibule, vestibular Space or cavity at the beginning of a canal; for example, the inner ear.

Vitamins Any of a number of organic substance that are essential for the normal growth and functioning of the body. Water soluble vitamins; B and C. Fat soluble vitamins; A, D, E, and K.

Vitiligo A condition in which there is an absence of natural pigment in sections of the skin or hair, that appears as whitish or light patch.

Wart A small dry growth on the skin. The condition is caused by a virus.

Wheeze Difficulty in breathing that is accompanied by a whistling sound.

White blood cell Leukocyte; a constituent of blood, formed in the bone marrow and the lymph glands. White blood cells defend the body against infection.

X-chromosome A sex chromosome; if a fetus has two X-chromosomes in its genetic make-up, it will develop as female.

Xeroderma A skin condition which produces excessively dry skin.

Xerophthalmia Extreme dryness of the eye.

Xerostomia Dry mouth.

Y-chromosome A sex chromosome; if a fetus has a Y-chromosome in its genetic make-up, it will develop as male.

Zoonosis An infection or infestation presents in animals that can be transmitted to man.

Index

A

- Abacavir 405
- Abdominal
 - colic 260
 - distention 92
- Abortion 249
- Absorption 19, 139
- Acamproste 274
- Acarbose 229
- ACE inhibitors 180
- Acebutolol 85, 88
- Acetaminophen 340
- Acetazolamide 165
- Acetic acid 470
- Acetylcholine 89, 91, 93, 278
- Acid
 - fast bacilli 437
 - resistant penicillin 367, 369
- Acidification of urine 18
- Acne 376
- Acridine 419
 - dyes 473
- Acriflavine hydrochloride 473
- Acrosoxacin 388
- Actinomycetes 358, 437
- Actinomycin D 446
- Actinomycosis 369
- Action of
 - amphetamine 81
 - drug 11
 - estrogens 239
 - insulin 225
- Acute
 - adrenal insufficiency 235
 - alcoholic intoxication 274
 - amebiasis 415
 - arthritis 351
 - asthmatic attack 86
 - barbiturate poisoning 297
 - bronchial asthma 78
 - gout 235, 351
 - intestinal amebiasis 418
 - iron poisoning 141
 - morphine poisoning 327
 - myocardial infarction 202
 - rheumatic fever 337
 - salicylate intoxication 339
 - severe asthma 135
 - toxicity 459
 - ulcerative gingivitis 416
- Acyl glucuronide 335
- Addison's disease 235
- Addisonian crisis 235
- Adenosine 199, 278
- Adrenal
 - gland 231
 - steroids synthesis 237
- Adrenaline 78, 79, 133
- Adrenergic
 - agonists 251
 - antagonists 83
 - drugs 75
 - neuron blockers 174
 - receptors 73
 - system 71
- Adrenoceptor agonists 75
- Adrenocorticotrophic hormone 211
- Adverse drug reaction and poisoning 50
- Adverse effect of
 - belladonna alkaloids 98
 - drugs in oral cavity 462
 - glucocorticoids 236
 - loop diuretics 163
 - oral iron 141
- Akinetic seizures 300
- Albendazole 426
- Albuterol 133
- Alcohol 271, 462, 470
- Alcopar 427
- Aldehydes 470
- Aldosterone 211, 231
- Alendronate 222
- Alfa-adrenoceptor blocking agents 202
- Alfentanil 328
- Alkalization of urine 18
- Alkaloid 5
- Alkanones 346
- Alkylating agents 446
- Allergic
 - diseases 235
 - reaction 163
- Allergy 227
- Allopurinol 353, 430
- Allylamine 411
- Alpha adrenergic blocking agents 83, 87
- Alprenolol 85
- Alteration in
 - concentration of drug 52
 - first pass metabolism 54
- Alteration of liver blood flow 55
- Aluminium 456
 - hydroxide 257
 - chloride solution 457
- Alzheimer's disease 283
- Amantadine 282, 406, 409
- Ambenonium 94
- Amebiasis 376, 415
- Amikacin 381, 396
- Amiloride 164
- Amine autacoids 117
- Amino acid conjugation 27
- Aminoglycosides 379
- Aminopenicillins 369
- Aminophylline 133
- Aminosidine 430
- Amiodarone 198
- Amiphenazole 332
- Ammonia silver nitrate 456
- Amoxicillin 369
- Amphetamine 81, 331, 332
- Amphotericin B 429
- Ampicillin 369
- Amrinone 186
- Anabolic steroids 244, 245
- Anaerobic infections 369, 378, 416
- Anaphylactic
 - reactions 78
 - shock 201, 202
- Androgen 244, 447
 - steroids 244
 - replacement therapy 244
- Angina 87, 188, 193
 - pectoris 191
- Anginal pain 189
- Angiotensin 125
 - converting enzyme 173, 177
 - receptor antagonist 173, 178
 - system 177
- Angiotensinogen 177
- Aniline dyes 455
- Anionic
 - system 29
 - transporter 29

- Anistreplase 153, 154
 Anorectic agents 82
 Anorexia 488
 Anorexiant 82
 Ansamycin 396
 Antacids 256
 Antagonists of leukotriene
 receptors 347
 synthesis 347
 Anterior pituitary hormones 209
 Anthelmintics 425
 Anthranilic acid derivatives 345
 Anthrax 384
 Antiamebic drugs 415
 Antiandrogen 245, 447
 Antianginal drugs 189
 Antianxiety 317
 Antiarrhythmic drugs 195
 Antibacterial spectrum 363, 369, 378,
 379, 383
 Antibiotics 5, 417, 423, 446
 Anticancer drugs 444
 Anticancerous action 36
 Anticholinergic
 agents 282
 drugs 95, 97
 Anticholinesterases 92, 93
 Antidepressants 310
 Antidiuretic
 drugs 167
 hormone 167, 212
 Antiemetics 260
 Antiestrogens 223, 240, 447
 Antifungal
 antibiotics 411
 drugs 411
 Anti-herpes viral agents 402
 Antihistamines 280
 Antihistaminics 117, 118, 130
 Antihyperlipidemic agents 147
 Antihypertensive drugs 171
 Anti-inflammatory drugs 134
 Anti-influenza viral agents 406
 Antimetabolites 413, 446
 Antimicrobial action 36
 Antimicrobials in diarrhea 268
 Antimony potassium tartrate 428
 Antimuscarinics 262
 Antiparkinsonian drugs 279
 Antiplatelet drugs 155, 189
 Antiprogestins 241
 Antipseudomonal penicillins 369
 Antipsychotic agents 318
 Anti-retroviral agents 404
 Antiseptics 461, 469
 Antisera 482
 Antispasmodics 268
 Antithrombotic agents 153
 Antithymocyte globulin 432
 Antithyroid 218
 drugs 214, 217
 Antitoxins 482
 Antiviral
 agents 407
 drugs 402
- Anxiety 87
 Apomorphine 280
 Apparent volume of distribution 24
 Aqueous solubility 20
 Arachidonic acid metabolites 277
 Aripiprazole 320
 Arrhythmias 87, 191
 Artemether 423
 Artemisinin 420, 423
 Arteries 150
 Arteriole
 dilators 187
 vasodilators 176
 Artesunate 423
 Aryl acetic acid derivative 343
 Ascorbic acid 489
 Aspartic protease enzyme 406
 Aspirin 156, 335, 460
 Astringents 156, 455, 456
 Atenolol 85, 86
 Atherosclerosis 189
 Atropine 97, 260
 substitutes 98
 Attention deficit hyperactivity disorder 81
 Atypical
 neuroleptics 125, 320
 pneumonia 376, 384
 Aureomycin 458
 Autoimmune disorders 431
 Autonomic
 control of heart 181
 ganglia 92
 innervations 67
 nerve endings 77
 nervous system 67
 Azapropazone 341
 Azithromycin 385
 Azoles 411, 413
 Aztreonam 372
- B**
- Bacampicillin 369
 Bacitracin 391, 392, 458
 Baclofen 106
 Bacterial
 gastroenteritis 366
 meningitis 378
 prostatitis 366
 sensitivity testings 358
 Bad breath 463
 Barbiturates 294, 296, 307
 Basophilic cells 207
 BCG vaccine 477
 Bed wetting 80, 313
 Benefits of combined pills 241
 Benign
 prostatic hypertrophy 85
 tertian 419
 Benserazide 282
 Benzhexol 99, 282
 Benzodiazepine 274, 291, 294, 305, 307,
 308
 antagonist 296
 Benzoic acid 414, 470
- Benzotropine 99, 282
 Benzyl penicillin 368
 Bephenium 427
 Beriberi 487
 Beta-adrenergic blockers 87
 Beta-arrestin kinase 43
 Beta-lactam antibiotics 367
 Beta-lactamase inhibitor 367, 370
 Betaxolol 88
 Bethanechol 92
 Bicuculline 332
 Biguanides 229
 Bile acid sequestrants 147
 Biliary
 colic 260
 excretion 29
 Bind to ribosomes 358
 Biosynthesis of thyroid hormone 214
 Biotin 489
 Biotransformation 25, 26
 Bipyridine derivative 186
 Bird flu 408
 Bismuth salts 258
 Bisoprolol 187
 Bisphosphonates 222
 Bithinol 428
 Bladder 76
 Bleaching
 agents 455
 powder 472
 Bleeding 372
 Bleomycin 447
 Blood
 brain barrier 17
 coagulation 151
 loss 202
 pressure 76, 171
 schizontocides 420
 vessels 76, 91
 Body
 aches 409
 compartments 23
 surface area 47
 temperature 98, 241
 Bone 121, 486
 marrow depression 447
 metabolism 220
 remodeling 220
 structure and composition 220
 Boric acid 470
 Botulism vaccine 480
 Bowman's capsule 161
 Bradycardia 86, 111
 Bradykinesia 279
 Brain 287
 Breast
 cancer 240, 447
 engorgement 249
 Bretylium 198
 Brilliant green 473
 Broad spectrum
 antibiotics 374
 drugs 357
 penicillins 367
 Bromhexine 130

- Bromocriptine 210, 282
 Bronchi 76
 Bronchial asthma 80, 98, 132, 235, 236, 333
 Bronchiolar smooth muscle 77
 Bronchodilators 75, 130
 Brucellosis 376, 381
 Bulk
 forming laxatives 265
 laxatives 265
 Bupivacaine 111
 Buprenorphine 329
 Bupropion 314
 Buspirone 124, 309
 Butorphanol 329
 Butoxamine 85
 Butyrophenones 320
- C**
- Calciferol 485
 Calcitonin 219, 222
 Calcium 220
 antagonists 191
 carbonate 257
 channel blockers 177, 180, 189, 191, 251
 disodium edetate 467
 hydroxide 455
 hypochlorite solution 472
 metabolism 233
 Campylobacter gastroenteritis 384
 Cancer 443
 chemotherapy 443
 Cannabinoids 333
 Capillary
 permeability 24
 structure 24
 Capreomycin 396
 Capsaicin 351
 Capsula glomeruli 161
 Carbachol 92
 Carbamazepine 28, 168, 304, 305
 Carbamylcholine 92
 Carbapenems 367, 372
 Carbenicillin 369
 Carbenoxolone 258
 Carbidopa 282
 Carbimazole 218
 Carbohydrate 484
 metabolism 225
 Carbolic acid 471
 Carbonic anhydrase inhibitors 165
 Carboxymethyl-cellulose 265
 Carboxypenicillins 369
 Carcinoma of breast 244
 Carcinoma prostate 240
 Cardiac
 action potential 181
 arrhythmias 195, 303
 failure 186
 glycosides 181, 183
 infarction 189
 stimulants 75
 Cardiogenic shock 200
- Cardiovascular
 effects 191
 system 76, 78, 108, 109, 297, 325
 Carminative mixture 255
 Carotene 485
 Carotenoids 485
 Carrier
 mediated transport 19
 molecules 38
 Carumonam 372
 Carvedilol 85, 87
 Cascade theory 150
 Castor oil 266
 Catabolic states 245
 Catecholamines 75
 Cationic
 system 29
 transporter 29
 Causes of
 hyperuricemia 352
 secondary hypertension 172
 Cefazolin's 371
 Cefoperazone 371
 Ceftazidime 371
 Ceftriaxone 371
 Cefuroxime 371
 Celecoxib 346
 Cell cycle 444
 nonspecific drugs 444
 specific drugs 444
 Cellular and molecular pharmacology 90
 Central
 anticholinergic drugs 280
 nervous system 107, 109, 331
 Centrally acting
 cough suppressants 130
 muscle relaxants 106
 Cephalixin 371
 Cephalosporins 367, 370
 Cephalothin 371
 Cephadrine 371
 Cerebral
 blood flow 286
 edema 235
 Cetavlon 471
 Cetrimide 471
 Cevix 241
 Chancroid 364, 366
 Charcoal 29
 Chemical transmission in nervous system 276
 Chemoprophylaxis 361, 398, 421
 Chemotherapeutic
 agents 4
 effect 36
 Chemotherapy 4, 357, 443
 Chemotherapy of
 cancer 443
 leprosy 399
 malaria 419
 tuberculosis 393
 urinary tract infections 389
 Chest pain 87
 Chickenpox 403
 Chills 409
- Chlamydial infections 376
 Chloral hydrate 298
 Chlorambucil 446
 Chloramphenicol 28, 377
 Chlorhexidine 462
 Chloride compounds 455
 Chlorinated lime 472
 Chlorine 461, 472
 Chloroguanide 423
 Chlorophyll 459
 Chloroquine 350, 417, 418, 421
 Chloroxylenols 461
 Chlorpromazine 262
 Chlorpropamide 168
 Cholecalciferol 485
 Cholera 387
 vaccine 479
 Cholestatic jaundice 384
 Cholestyramine 29, 147
 Cholinergic
 drugs 92
 nerve 89
 receptors 89
 system and drugs 89
 Cholinesterases 89
 Cholinomimetic alkaloids 92
 Chronic
 adrenal insufficiency 235
 amebiasis 415, 418
 gout 351
 pulpitis 340
 salicylate poisoning 339
 toxicity 459
 Cimetidine 257
 Cinchona alkaloids 419
 Ciplin 365
 Ciprofloxacin 387
 Circadian rhythm 231
 Cisapride 124, 263
 Cisplatin 447
 Clarithromycin 384, 400
 Classical angina 189
 Classification of
 androgen 244
 antiemetic 261
 antiepileptic drugs 301
 antimalarial drugs 419
 antimicrobial agents 357
 antithyroid drugs 218
 autacoids 117
 drugs 416
 drugs used in
 gout 352
 leishmaniasis 429
 malignancy 444
 epilepsy 299
 fungal infection 411
 H₁ blockers 118
 local anesthetics 107
 penicillins 367
 Clavulanic acid 370, 373
 Clindamycin 391
 Clinical
 pharmacokinetics 30
 pharmacology 4

- use of
 - bromocriptine 210
 - iron 140
 - vasopressin and analogues 213
 - Clofazimine 400
 - Clofibrate 168, 149
 - Clomiphene citrate 240
 - Clonazepam 305
 - Clonidine 78, 174, 326
 - controls diarrhea 174
 - Clotrimazole 413
 - Clove oil 461
 - Clozapine 125, 320
 - CNS
 - depressant 273
 - depression 53
 - stimulants 75, 331
 - Cobra
 - bite 95
 - venom 95
 - Cocaine 331, 332
 - Codeine 267, 327, 460
 - Colchicine 352
 - Cold
 - box 482
 - chain 482
 - extremities 86
 - Colistin 392
 - Collagen diseases 235
 - Colloidal silver compound 474
 - Colloids 203
 - Colony-stimulating factors 144
 - Combination of
 - antimicrobials 360
 - drugs in angina 192
 - Combined pills 242
 - Common phenothiazine derivatives 318
 - Complex partial seizures 300
 - Complications of spinal anesthesia 112
 - Conformational distortion theory 287
 - Congenital adrenal hyperplasia 235
 - Congestive cardiac failure 85, 182, 186
 - Conjunctivitis 364
 - Constipation 265, 488
 - Contact dermatitis 51
 - Contraindication to
 - anticoagulant therapy 153
 - combined pill 241
 - glucocorticoid therapy 236
 - heparin therapy 152
 - spinal anesthesia 112
 - thrombolytic therapy 155
 - Control of hemorrhage 78
 - Copper 456
 - sulphate 456
 - Cornea membrane 21
 - Coronary
 - blood flow 188, 189
 - circulation 191
 - Corpus cavernosum 246
 - Correction of acidosis 275
 - Cortex 207
 - Cortical focal epilepsy 300
 - Corticosteroids 202, 231, 262
 - Corticotropin releasing factor 209
 - Cotrimoxazole 363, 364
 - Cough 129, 327, 409
 - Cresol 456, 471
 - Crippling inflammatory disorder 348
 - Cromolyn sodium 134
 - Crystalline zinc insulin 227
 - Crystalloids 203
 - Crystalluria 364
 - Curare poisoning 95
 - Cushing syndrome 242
 - Cutaneous vasodilatation 273
 - Cyanocobalamin 489
 - Cyclophosphamide 446
 - Cyclopirox olamine 414
 - Cycloserine 396
 - Cyclosporine 351, 431
 - Cyproheptadine 124
 - Cyproterone acetate 245
 - Cytarabin arabinoside 446
 - Cytolytic reactions 51
 - Cytotoxic
 - drug 432, 443
 - effect 36
- ## D
-
- Dacarbazine 446
 - Daidzine 274
 - Dakin's solution 472
 - Dale's
 - phenomenon 76
 - vasomotor reversal 76
 - Dalfopristin 392
 - Damage cell membrane 358
 - Danazol 155, 245
 - Dantrolene 106
 - Dapsone 399
 - Daunorubicin 446
 - Decreasing uterine motility 240
 - Decubitus ulcer 274
 - Deferiprone 468
 - Dehydration 163
 - Dehydroemetine 416, 417
 - Deltoid muscle 14
 - Demecarium 94
 - Dementia 283
 - Dental
 - caries 458
 - drug 453
 - plaque 458
 - Dentifrices 453
 - Deodorant 469
 - Depolarising blockers 105
 - Deprenyl 282
 - Dermojet injection 13
 - Desferrioxamine 468
 - Desflurane 289
 - Detergents 453
 - Dettol 471
 - Dexfenfluramine 82, 124, 332
 - Dextran 202, 203
 - Dextromethorphan 330
 - Dextropropoxyphene 328
 - Dextrose 204
 - Dhatura 98
 - Diabetes mellitus 224
 - Diabetic ketoacidosis 227
 - Diaminopyrimidine 419
 - Diarrhea 326, 372
 - Diazepam 106, 291, 294, 306
 - Diazoxide 176
 - Dibucaine 111
 - Diclofenac 343
 - Dicyclomine 260, 262
 - Didanosine 405
 - Diethylcarbamazine 427
 - Diffunisal 338
 - Digitoxin 184, 185
 - Digoxin 184, 185, 199
 - Dilling's formula 47
 - Diloxanide furoate 416, 417
 - Diltiazem 198
 - Dimercaprol succimer 467
 - Dimethicone 255
 - Diphenoxylate 268, 328
 - Diphenyl-hydantoin 302
 - Diphtheria 369, 384
 - vaccine 478
 - Dipyridamole 156, 192
 - Directly acting
 - muscle relaxants 106
 - sympathomimetics 75
 - Disease modifying drugs 348
 - Disease of lightening 299
 - Disfavor fertilization 243
 - Dismenorrhea 98
 - Disopyramide 196
 - Disorders of bones 221
 - Disprin 460
 - Distal convoluted tubule 162
 - Distribution of
 - iron in body 139
 - sympathetic system 71
 - Disulfiram 28, 274, 372
 - DNA viruses 402
 - Dobutamine 78, 80
 - Docebenone 347
 - Doloxifene 240
 - Domperidone 263
 - Donepezil 94
 - Dopamine 78, 79, 277
 - Doxapram 332
 - Doxazosin 83
 - Doxorubicin 446
 - Doxycycline 377, 420, 423
 - D-penicillamine 349
 - Dracunculosis 416
 - Droperidol 291
 - Drug
 - action on 5-HT receptors 124
 - affecting hematopoiesis 139
 - allergy 51
 - controller of India 8
 - dependence 52
 - destroying thyroid tissue 218
 - distribution 23
 - effects on neurohumoral transmission 74
 - for
 - constipation and diarrhea 265
 - iron deficiency anemia 140

leishmaniasis 429
 megaloblastic anemias 141
 trypanosomiasis 429
 formulations 12, 60
 induced diseases 50
 information sources 4
 inhibit
 hormone release 218, 219
 iodine trapping 218
 interaction 54, 153
 metabolism 25
 nomenclature 5
 of choice 433
 preparations for hypothyroidism 217
 protein binding displacement 55
 resistance 52
 structure 24
 transport across membrane 19
 used for treatment of moderate pain 460
 used in
 acute attacks 125
 dental hemorrhage 457
 disorders of coagulation 150
 Parkinson's disease 279
 psychiatric disorders 316
 rheumatoid arthritis 348
 sexual impotence 246
 therapy of shock 202
 tuberculosis 393
 used in treatment of
 angina pectoris 188
 diarrhea 267
 migraine 125
 non-productive cough 130
 oral inflammation 460
 productive cough 129
 rheumatoid arthritis 348
 withdrawal reaction 50
 Dry mouth 462
 Dysfunctional uterine bleeding 240
 Dysmenorrhea 240
 Dyspepsia 255
 Dystrophic diseases 458

E

E. coli 371
 Echthiophate 94
 Econazole 413
 Ecosprin 460
 Edema 163, 227
 Edrophonium 94
 Efavirenz 406
 Efflux pump 359
 Eflornithine 430
 Eicosanoids 120
 Electroconvulsion therapy 316
 Electrophysiological activity 185
 Emergency pills 243
 Emetics 260
 Emetine 416, 417
 Eminase 153
 Empirical therapeutics 3
 Endocrinal glands 207
 Endocytosis 19
 Endogenous
 ligands 323
 pathways 145
 Endometrial carcinoma 241
 Endometriosis 241
 Endorphin 323
 Enflurane 289
 Enkephalin 323
 Enoxacin 388
 Enteramine 123
 Enteric fever 387
 Enterohepatic circulation 25, 27, 28
 Enzymatic
 induction 28, 38
 inhibition 28
 stimulation 38
 Enzyme
 induction 55
 inhibition 55
 Ephedrine 78, 80, 133
 Epilepsy 81, 299
 during pregnancy 306
 Epsilon aminocaproic acid 155
 Equilibrium 83
 Ergocalciferol 485
 Ergometrine 249
 Ergot alkaloids 83, 84, 123, 125
 Ergotamine 83, 125
 Erythromycin 28, 383, 458
 Erythropoietin 143
 Erythrosin 457
 Esmolol 85, 87, 198
 Esophageal reflux 92
 Esters of choline 92
 Estrogen 223, 238, 241, 447
 Etanercept 351
 Ethambutol 395
 Ethanol 271, 275
 Ether 288
 Ethionamide 395, 400
 Ethosuximide 304, 305
 Ethyl
 alcohol 271, 470
 glycol poisoning 274
 stibamine 429
 Etidocaine 110
 Etodolac 345
 Etomidate 290
 Euphoria 273
 Evacuant enema 16
 Ex vivo gene therapy 62
 Exaggerated adrenergic activity 171
 Exceptions to BBB 18
 Excitatory
 amino acids 277
 effect 325
 Exogenous pathways 145
 Expectorants 129
 Extemporaneous expectorant formulation 129
 Extended spectrum penicillins 367, 369
 Extracardiac effects 185, 191
 Extrinsic
 asthma 132
 system 150

Eye 92
 diseases 235
 infections 378

F

Factors affecting
 absorption 20
 bioavailability 22
 drug metabolism 28
 Factors
 deciding routes of administration 11
 for coagulation 150
 governing volume of drug distribution 24
 influencing oral anticoagulant activity 153
 modifying dosage and drug action 47
 regulating blood pressure 171
 responsible for
 CCF 183
 hyper-prolactinemia 210
 Falciparum malaria 387
 Famciclovir 404
 Familial hypercholesterolemia 147
 Famotidine 257
 Fast neurotransmitters 276
 Fat soluble vitamins 485
 Father of modern chemotherapy 357
 Fatigue 409
 Fats 484
 Febrile convulsions 305
 Fecal softeners 265
 Feces 29
 Felbamate 305
 Fenfluramine 82
 Fenoprofen 344
 Fentanyl 291, 328
 Ferric
 chloride 456
 sulfate solution 457
 Fetal
 alcohol syndrome 274
 hydantoin syndrome 303
 Fever 337, 409
 Fibric acid derivatives 149
 Fibrin formation 151
 Fick's law 18, 285
 Filgrastim 144
 Filling root canal 459
 Finasteride 245
 Flare 118
 Flecanide 197
 Fluconazole 414
 Flucytosine 413
 Fludrocortisone 237
 Flu-like syndrome 394
 Flumazenil 296
 Fluorescein dye 457
 Fluorides 455
 Fluoroquinolones 386, 396
 Fluoxetine 274, 313
 Flurazepam 296
 Flurbiprofen 345
 Flutamide 245

Folate
 antagonists 419
 deficiency 365
 Folic acid 141
 Folinic acid 275
 Follicle stimulating hormone 211
 Fomepizole 275
 Forced diuresis 163
 Formal therapeutic trial 9
 Formaldehyde 455, 470
 Formed elements of blood 233
 Formoterol 133
 Forms of gene therapy 61
 Foscarnet 404
 Fostestrol 447
 Frusemide 162
 Fulminating hepatitis 305
 Fungi 358, 438
 Fusidic acid 391, 392

G

Gabapentin 305
 Gametocidal drugs 420
 Ganciclovir 403
 Ganglion blockers 97, 174
 Gas gangrene 369
 Gastric emptying time 20
 Gastrointestinal
 diseases 235
 tract 77
 Gelatin
 foam 156
 products 203
 sponge 457
 Gemfibrozil 149
 Gene transfer vectors 62
 General
 anesthesia 284
 considerations 285, 348
 Genetically engineered proteins 61
 Genitourinary smooth muscle 77
 Gentamicin 381
 Germ-line gene therapy 61
 Giardiasis 416, 418
 Gingival
 hyperplasia 302, 463
 hypertrophy 463
 retraction cords 457
 GIT
 disorders 20
 disturbances 163
 Glands 118
 Glaucoma 78, 87, 92
 Glomerular filtration rate 79
 Glucagon 202, 230
 Glucocorticoids 134, 207, 211, 223, 233, 432, 447
 Glucuronide 335
 Glutamate 277
 Glutaraldehyde 470
 Glutathione conjugation 27
 Gluteal muscle 14
 Glycerol 166
 Glycine conjugation 27

Gold salts 349
 Gonadotrophin releasing hormone 209
 Gonococcal ophthalmia neonatorum 473
 Gonorrhea 369, 372, 384
 Gram-negative
 bacilli 435
 infections 372
 Gram-positive bacilli 434
 Grandmal epilepsy 303
 Granisetron 262
 Grave's disease 218
 Gray-body syndrome 378
 Griseofulvin 412
 Growth
 hormone releasing hormone 209
 stimulation in children 245
 Guanbenz 174
 Guanethidine 174
 Gum 5
 paints 462

H

H. influenzae 371
 H. pylori infections in peptic ulcer 416
 H₂ receptor blockers 257
 Halitosis 463
 Hallucinogens 331
 Halofantrine 422
 Halogenated hydroxyquinolines 416, 417
 Halogens 461, 472
 Haloperidol 320
 Halothane 289
 Hamycin 412
 Hard soap 453
 Hasten uterine involution 249
 Hazards of immunization 482
 Headache 333, 409
 Heart 191
 diseases 369
 rate 185
 Heat 470
 regulation 325
 shock proteins 45
 Helminths 425
 Hematinics 139
 Hemophilus infection 387
 Hemorrhagic fever 407
 Hemostasis 150
 Henderson-Hasselbach's equation 18
 Henle's loop 162
 Heparin 151
 antagonist 152
 Hepatic
 amebiasis 418
 clearance 31
 Hepatitis
 A vaccine 480
 B vaccine 481
 Heroin 327
 Herpes simplex virus infections 403
 Hetrazan 427
 Hexachlorophene 462, 472
 Highly purified insulins 228
 Hirudin 152
 Histamine 117
 substitutes 118
 HMG-CoA reductase inhibitors 148
 Hofmann elimination of drug 28
 Hormonal contraceptives 242
 Hormone 5, 45
 affecting
 metabolism 207
 reproductive system 207
 in cancer chemotherapy 447
 replacement therapy 240, 241
 Human
 albumin 203
 chorionic gonadotropins 212
 fibrin foam 457
 insulins 227
 interferon's 407, 431
 menopausal gonadotropins 212
 Huntington's disease 319
 Hydralazine 176
 Hydrogen peroxide 462, 473
 Hydroxychloroquine 350
 Hydroxyethyl starch 203
 Hydroxytryptamine 123
 Hydroxyzine 310
 Hyoscine 262
 butyl bromide 260
 Hypercalcemia 163
 Hyperglycemia 163
 Hyperkalemia 163
 Hyperlipidemia 145, 163
 Hyperlipoproteinemias 147
 Hyperparathyroidism 222
 Hyper-prolactinemia 210
 Hypersensitivity reaction 109
 Hypertension 85, 163, 171, 191
 Hypertensive crisis 179
 Hyperuricemia 163
 Hypervitaminosis 485
 Hypnotic 293, 326
 Hypocalcemia 163
 Hypochlorous acid 472
 Hypoglycemia 227
 Hypokinesia 279
 Hypomagnesemia 163
 Hyponatremia 163
 Hypotension 80, 111
 Hypothalamic hormones 207, 209
 Hypovolemia 163
 Hypovolumic shock 200

I

Ibuprofen 335, 344
 Idiopathic disorder 316
 Idiosyncrasy 51
 Idoxuridin 403
 Ifosfamide 446
 Imidazoles 413
 Imipenem 372
 Imperial system 59
 Importance of blood flow 23
 Important terminology 40

- In vitro
 experiments 7
 fertilization 240
- In vivo
 experiments 7
 gene therapy 62
- Increased peripheral resistance 172
- Indication of
 GH 210
 insulin 227
- Indinavir 406
- Indirectly acting sympathomimetics 75
- Indole acetic acid derivatives 341
- Indomethacin 167, 341
- Infertility in females 240
- Inflammatory
 bowel diseases 268
 diseases 458
- Influence iron absorption 140
- Influenza vaccine 481
- Inhalation
 anesthetics 291
 steroids 235
- Inhaled steroids 134
- Inhibit
 cell wall synthesis 358
 DNA
 functions 358
 gyrase 358
 synthesis 358
 protein synthesis 358
- Inhibitory
 amino acids 277
 hormones 207
- Injury to research subject 8
- Insomnia 296
- Insulin 224, 230
 analogus 228
 dependent diabetes mellitus 224
 resistance 228
- Intermediate acting barbiturates 296
- Intestinal
 colic 260
 motility 20
- Intestine 486
- Intra-arterial administration 15
- Intra-articular injections 15
- Intramedullary administration 15
- Intraperitoneal administration 14
- Intravenous
 anesthetics 289
 magnesium sulfate 251
- Intrinsic
 asthma 132
 system 150
- Iodides 219
- Iodine 461
 ointment 472
 stain 455
- Iodoform 456
- Iodophors 472
- Iodoquinol 417
- Ion
 channels 37
 trapping 29
- Ionic inhibitors 218
- Iontophoresis 455
- Ipratropium bromide 99
- Iron 139, 456
 deficiency anemia 140
 stain 456
- Irreversible anticholinesterases 95
- Irritable bowel syndrome 268
- Ischemic heart diseases 87
- Isoflurane 289
- Isolated systolic hypertension 171
- Isoniazid 394
- Isophane insulins 227
- Isoprenaline 78, 79, 133
- Isopropyl alcohol 470
- Itraconazole 414
- Ivermectin 427
-
- J**
- Jarisch-Herxheimer reaction 368
-
- K**
- Kallikreins 126
- Kanamycin 381, 396, 458
- Keratoconjunctivitis 403
- Ketamine 290
- Ketanazole 28
- Ketanserin 83, 124
- Ketoconazole 414, 430
- Ketoprofen 344
- Ketorolac 343
- Ketotifen 135
- Kidney 121, 287, 332, 486
- Kininogen 126
- Kinins 126
- Kirby-Bauer technique 358
- Korsakoff's psychosis 273, 488
-
- L**
- Labetalol 85, 87
- Lactobacillus acidophilus 268
- Lamivudine 405
- Lamotrigine 305
- Lansoprazole 258
- L-asparaginase 447
- Lead acetate 456
- Leflunomide 350
- Left ventricular hypertrophy 178
- Legionnaire's pneumonia 384
- Leishmaniasis 429
- Lente insulins 227
- Lepra reactions 401
- Lepromatous leprosy 387, 399
- Leptazol 332
- Leptospirosis 376
- Leptazol 301
- Leukotriene 122
 pathway inhibitors 135
- Levamisole 427
- Levodopa 280
- Levofloxacin 388
- Lidocaine 110, 461
- Lignocaine 197
- Limitations of erythromycin 384
- Lincomycin 391
- Linezolid 391, 392
- Lipid
 derivative autacoids 117
 soluble drugs 18
- Lipodystrophy 227
- Lipophilic antioxidants 149
- Liquid formaldehyde 456
- Lithium carbonate 314
- Liver 287
 diseases 235
- Location of
 ganglia 71
 preganglionic neurons 71
- Lomefloxacin 388
- Loop diuretics 162
- Loperamide 268
- Lorazepam 291
- Losartan 178
- Lovastatin 148
- Low
 molecular weight heparins 152
 WBC count 372
- Loxatidine 257
- Lugol's solution 472
- Lung 29
 diseases 236
- Luteinizing hormone 211
- Lymphogranuloma venereum 364
- Lysol 471
-
- M**
- Macrolides 383
- Magnesium salts 257
- Malaria 364, 376, 421
- Male
 contraceptives 245
 infertility 240
- Malignant tertian 419
- Mammary gland 241
- Management of
 acute attack 135
 chronic asthma 135
 dental hypersensitivity 455
 drug overdoses and poisoning 53
- Mandelamine 389
- Mandl's paint 472
- Mania 319
- Mast cell stabilizers 134
- Mazindol 82
- Measurement of anxiolytic activity 307
- Mebendazole 426
- Mechanism of action of
 ACE inhibitors 178
 antiepileptic drugs 301
 oral contraceptives 243
- Mechanism of
 pain and nociception 321
 variation in drug responsiveness 52
- Mechlorethamine 446
- Mecroxalol 87
- Medulla 207
- Mefloquine 422
- Megaloblastic anemia 141, 302, 365

- Meglumine antimonate 429
 Melarsoprol 430
 Melatonin 278
 Melfalan 446
 Meningitis 18, 369, 381
 Meningococcal infections 368
 Menstrual
 benefits 241
 disorder 241
 Menthol 461
 Meperidine 328
 Mephesisin 106
 Mephenteramine 81
 Mepivacaine 110, 461
 Meprobamate 307
 Mercuric chloride 456
 Mercury compounds 473
 Mesalamine 338
 Metabolic effects of insulin deficiency 226
 Metabolism of angiotensins 126
 Metachlopromide 124
 Metallic astringent 456
 Metamizol 341
 Metaraminol 81
 Methanol 274, 275
 Methenamine mandelate 389
 Methohexitone 290
 Methotrexate 350, 446
 Methoxamine 81
 Methoxyflurane 289
 Methyl
 alcohol 275
 ergometrine 249
 Methylcellulose 265
 Methylene blue 473
 Methylpolysiloxane 255
 Methylxanthines 133, 166, 278, 331, 332
 Methysergide 124
 Metoclopramide 263
 Metocurine 104
 Metoprolol 85, 86, 187
 Metrology 59
 Metronidazole 360, 416, 418
 Mevastatin 148
 Mexiletine 197
 Meyer Overton theory 287
 Michaelis-Menten kinetics 32
 Miconazole 414
 Microsomal
 conjugations 27
 enzymes 27
 hydrolysis 27
 reduction 27
 Midazolam 291
 Mifepristone 241
 Migraine 87, 125, 191
 Mild
 asthma 135
 hypertension 171
 Milk ejection 249
 Milrinone 186
 Mineralocorticoid 207, 237
 action 233
 Minerals 5, 484, 485
 Minimal alveolar concentration 285
 Minimum
 bactericidal concentration 358
 inhibitory concentration 358
 Mini-pill 243
 Minocycline 377, 400
 Minoxidil 176
 Mithramycin 447
 Mixed acting sympathomimetics 75
 MMR vaccine 480
 Moderate
 asthma 135
 hypertension 171
 Monoamine
 oxidase inhibitors 311
 theory of depression 310
 Monobactams 367, 372
 Montoux test 478
 Mood-altering stabilizing drugs 314
 Morning sickness 489
 Morphine 324
 Motion sickness 262
 Mouthwashes 456
 Multi-antibiotic resistant infections 387
 Multibacillary leprosy 400
 Multi-compartment pharmacokinetics
 model 23
 Multiple antibiotics resistance 360
 Mummifying agents 456
 Mupirocin 391, 392
 Muromonab CD₃ 432
 Muscarinic
 actions 91
 receptors 89
 Muscle relaxants 104
 Musculoskeletal disorders 106
 Myasthenia gravis 94
 Mycobacterium leprae 399
 Mydriasis 80
 Myleran 446
 Myocardial
 contractility 184
 contraction 182
 infarction 87, 178, 193
 oxygen consumption 185
 Myoclonic seizures 300
 Myxedema 217
- ## N
- Nabumetone 346
 Nadolol 85, 87
 Nalbuphine 329
 Nalidixic acid 386
 Nalmefene 274
 Nalorphine 329
 Naloxone 329
 Naltrexone 274, 330
 Naproxen 344
 Narcolepsy 80, 81
 Narcotic
 analgesics 321, 323
 antagonists 321
 Narrow
 angle glaucoma 92
 spectrum drugs 357
 Nasal decongestants 75, 80, 82
 Natriuresis 162
 Natural
 alkaloid 97
 androgen 244
 penicillins 367, 368
 Nature of
 drugs 5
 epilepsy 299
 schizophrenia 316
 Nedocromil 135
 Nelfinavir 406
 Nematodes 425
 Neomycin 381
 Neoplastic diseases 458
 Neostigmine 94
 Nephron 161
 Nephrotoxicity 372, 380, 412
 Netimicin 381
 Neurocysticercosis 428
 Neuro-degenerative disease 279
 Neurohumoral transmission 68
 Neuroleptic analgesia 291
 Neuromodulators 276
 Neuromuscular
 blockade 380
 blockers 97, 104
 junction 92, 103
 Neuropathic pain 322
 Neurophysiology of epilepsy 301
 Neurotransmitters of sympathetic system 71
 Neurotrophic factors 276
 Neutral transporter 29
 Nevirapine 406
 Newer non-sedative antihistaminics 119
 Niacin 148, 488
 Niclosamide 428
 Nicorandil 192
 Nicotinic
 acid 148, 488
 actions 92
 receptors 89
 Nifedipine 191
 Nifurtimox 430
 Nikethamide 332
 Nimesulide 346
 Niridazole 428
 Nitrates 189
 Nitric oxide 277, 278
 Nitrofurantoin 389
 Nitroimidazoles 416
 Nitroprusside 176
 Nitrous oxide 287
 Nocardiosis 364
 Nocturnal enuresis 80, 81
 Nonacetylated salicylates 338
 Nonbarbiturate sedative hypnotics 298
 Non-catecholamines 75, 80
 Non-insulin dependent diabetes mellitus 224
 Non-ligand gated ion channels 37
 Non-microsomal
 enzymes 27
 hydrolysis 27
 reduction 27

- Non-nucleoside reverse transcriptase inhibitor 406
- Nonopioid antitussives 330
- Nonsedative antihistaminics 119
- Nonsteroidal
 anti-inflammatory drugs 334, 348
 estrogen antagonist 243
- Non-systemic antacids 257
- Noradrenaline 79, 277
- Noradrenergic transmission 71
- Norfloxacin 388, 420, 423
- Nosocomial infections 372
- Nucleoside reverse transcriptase inhibitors 404
- Nutritional rickets and osteomalacia 223
- Nystatin 412
- O**
- Obesity 81
- Obstructive cardiomyopathy 87
- Obtundents 454
- Octreotide 209
- Octrider 209
- Ofloxacin 388, 400
- Olanzapine 320
- Oligozoospermia in male 240
- Omeprazole 258, 264
- Ondansetron 125, 262
- Open angle glaucoma 92
- Opiates 322
- Opioid 292
 analgesics 322
 receptors 323
- Opium 322
- Optic neuritis 395
- Oral
 anticoagulants 152
 cavity 462
 contraceptive 238, 240
 preparations 242
 hypoglycemic drugs 229
 infections induced 463
 inflammation 460
 pain 460
 pills 242
 route 13
 ulceration 463
- Organ transplantation 236
- Organophosphorus poisoning 96, 98
- Ornidazole 416
- Orphan drug 6
- Oseltamivir 410
- Osmotic
 diuretics 165
 purgatives 265, 266
- Osteoarthritis 235, 338
- Osteomalacia 221, 302
- Osteomyelitis 381
- Osteopenia 221
- Osteoporosis 221, 240
- Ototoxicity 163, 380
- Ovarian suppression 241
- Oxaminiquine 428
- Oxaprozine 345
- Oxicams 346
- Oxidative stress 278
- Oxidising agents 455
- Oxidized cellulose 457
- Oxprenolol 85
- Oxymetazoline 78
- Oxyphenonium 260
- Oxytocin 249
- P**
- Pain and swelling of salivary glands 463
- Pamidronate 222
- Pantothenic acid 488
- Papaverine 246
- Para-amino
 hippurate 29
 salicylic acid 395
- Paracetamol 340
- Paraform 456
- Paraldehyde 298, 306
- Paramomycin 430
- Paranoid states 319
- Parathyroid hormone 221
- Parenteral
 iron 141
 routes 11
- Parkinson disease 279
- Paromomycin 417
- Paroxetine 314
- Paucibacillary leprosy 400
- Pefloxacin 388
- Penicillin 29, 78, 367
 G 18, 368
 prophylaxis 369
- Penicillinase resistant penicillins 367, 369
- Pentamidine isothionate 429
- Pentazocine 329, 460
- Pentoxifylline 155
- Peptic ulcer 98, 255, 256
- Peptide
 autacoids 117
 hormones 208
- Peptidoglycan 367
- Pergolide 282
- Periodontal
 abscess 340
 diseases and management 458
- Peripheral
 neuritis 394
 vascular disease 85, 191
- Peripherally acting skeletal muscle relaxants 104
- Peritonitis 381
- Pertussis vaccine 478
- Petitmal epilepsy 299
- Pharmacological actions of acetylcholine 91
- Pharmacology of vitamin K 156
- Pharmacopoeia 4
- Pharmacotherapy of
 angina 192
 gout 351
- Pharmacovigilance 4
- Phenobarbital 28
- Phenobarbitone 303, 306
- Phenolphthalein 266
- Phenothiazine 318
 derivatives 292
- Phenoxybenzamine 83
- Phentolamine 83, 84
- Phenylbutazone 341
- Phenylephrine 81
- Phenylpropanolamine 82
- Phenytoin 28, 197, 305, 306
 sodium 302
- Pheochromocytoma 85, 87
- Phosphate 221
- Phosphodiesterase inhibitors 186
- Phylloquinone 487
- Phylum
 nematelminthes 425
 platyhelminthes 425
- Physiology of urine formation 161
- Physostigmine 94
- Picrotoxin 332
- Pilocarpine 92
- Pindolol 85, 88
- Pinocytosis 19
- Pioglitazone 229
- Pipenzolate 260
- Piperazine citrate 427
- Pirenzepine 99
- Piriprost 347
- Piroxicam 346
- Pituitary
 gland 241
 hormones 207
- Placebo controlled 10
- Placental hormones 207
- Plague 376, 381, 387
 vaccine 479
- Plain mouthwashes 460
- Plasma
 concentration 30
 expanders 203
 lipid levels 145
 protein binding 25
- Platelet activating factor 120, 122
- Plicamycin 447
- Pneumococcal infections 368
- Pneumocystis carinii infection 366, 429
- Pneumonia 381, 387
- Poliomyelitis vaccine 480
- Polydypsia 224
- Polygenic hypercholesterolemia 147
- Polymyxin 392
 B 458
- Polypeptide antibiotics 391, 392
- Polyphagia 224
- Polyurea 224
- Polyvinyl pyrrolidone 203
- Postcoital
 contraceptive 242
 pill 243
- Posterior pituitary hormones 212
- Postmyocardial infarction 338
- Postoperative paralytic ileus 95
- Postpartum
 hemorrhage 249
 lactation 241

Postponement of menstruation 241
 Postural hypotension 172
 Potassium
 channel openers 189, 192
 nitrate 455
 permanganate 473
 sparing diuretics spironolactone 164
 Povidone-iodine 462
 Pralidoxime 96
 Pravastatin 148
 Praziquantel 428
 Prazosin 83, 85
 Preanesthetic medication 291
 Preparations of
 anabolic steroids 245
 insulin 227, 228
 iron 140
 Prevention of drug absorption 53
 Prilocaine 110
 Primaquine 422
 Primary hypertension 171
 Prinzmetal's angina 189
 Procainamide 196
 Procaine 110, 461
 Procarbazine 447
 Prochlorperazine 262
 Productive cough 129
 Proflavine hemisulphate 473
 Progestins 240, 241, 447
 Progesterone-only pills 243
 Proguanil 423
 Prokinetic agents 263
 Prolactin 210
 Prolactin releasing factor 209
 Propafenone 197
 Propantheline 260
 Prophylaxis 87, 223
 Propionic acid derivatives 344
 Propiphenazone 341
 Propofol 290
 Propoxyphene 328
 Propranolol 85, 192, 198
 Propylthiouracil 218
 Prostaglandin 120, 250
 analogues 259
 Prostatic carcinoma 447
 Protamine
 sulphate 152
 zinc insulin 227
 Protein 484
 bound iodine 218
 Proton pump inhibitors 258
 Prototype drug 97
 Protozoal infections 376
 Proximal tubule 162
 Pseudocholinesterase 89
 Pseudomonas infections 387
 Psychomotor
 epilepsy 300
 seizures 303
 stimulants 332
 Psychoses 316
 Psychotics 316
 Psychotomimetic drugs 331, 333

Pulmonary
 blood flow 286
 ventilation 286
 Pyrantel pamoate 426
 Pyrazinamide 394
 Pyrazolon derivatives 341
 Pyridostegmine 94
 Pyridoxine 488
 deficiency 489
 Pyrimethamine 422

Q

Quadruple reassortant 409
 Quaternary ammonium compounds 462
 Quetiapine 320
 Quinidine 196
 Quinine 421
 Quiniodochlor 417
 Quinolones 386
 Quinupristin 392

R

Rabies vaccine 481
 Racemic isomer 427
 Radioactive iodine 219
 Raloxifene 240
 Ranitidine 257
 Rasagiline 282
 Rebound hypertension 86
 Recent arrived branches in pharmacology 4
 Receptor
 mediated action 40
 occupation theory 38
 regulation 40
 Recombinant
 DNA technology 5
 tissue type plasminogen activator 153
 Red thrombus 150
 Regulation of
 secretion 210, 244
 ion channels 44
 Relative refractory period 181
 Releasing hormones 207
 Removal of absorbed drug 53
 Renal
 diseases 178, 235
 excretion 28
 toxicity 376
 Replacement therapy 235, 240
 Reserpine 175
 Resins 5
 Resistance to antimicrobial agents 359
 Resistant tuberculosis 397
 Resorcinol 471
 Resperidone 125
 Respiration 76, 241
 Respiratory
 failure 111
 stimulants 331
 system 78, 297
 tract infections 366, 369
 Retroviral protease inhibitors 406

Reversal of
 cholinesterase inhibition 96
 neuromuscular blockade 105
 Reye's syndrome 339
 Rheumatic
 carditis 235
 fever 369
 Rheumatoid arthritis 235, 338
 Ribavirin 407
 Riboflavine 488
 Rickets 221
 Rickettsial infections 376, 378
 Rifabutin 396
 Rifampicin 393, 396, 400
 Rifampin 393
 Rimantadine 406, 409
 Ring worm 411
 Risperidone 320
 Ritonavir 406
 Rivastigmine 94
 RNA viruses 402
 Role of
 carbohydrate and acids 458
 glucocorticoids 398
 Root canal therapy 459
 Rosiglitazone 229
 Roxatidine 257
 Roxithromycin 384

S

Salbutamol 78, 133
 Salicylic acid 414
 Salicylates 335
 Salicylic acid 335
 Salicyluric acid 335
 Salmeterol 133
 Salmonella infections 387
 Salts of zinc 456
 Salturesis 162
 Saralasin 178
 Sargramostim 144
 Schistosomiasis 428
 Schizophrenia 319
 Seasonal flu 409
 Secnidazole 416
 Secretory glands 92
 Selection of antibacterial agent 361
 Selective serotonin hydroxytryptamine reuptake
 inhibitors 313
 Selegiline 282
 Selenium sulfide 414
 Semisynthetic penicillins 369
 Senile
 osteoporosis 223, 245
 vaginitis 240
 Septic shock 200, 202
 Septicemia 369, 381
 Septran 365
 Seroquel 320
 Serotonin 123
 agonists 124
 antagonists 124
 Sertindole 320

- Sertraline 314
 Sevoflurane 289
 Sex steroids 207
 Sexually transmitted diseases 376
 Sildenafil 246
 Silver 456
 compounds 473
 nitrate 455, 456, 459, 473
 stain 455
 sulfadiazine 473
 Simvastatin 148
 Sisomicin 381
 Skeletal muscles 77, 105, 232, 244, 297, 333
 Skin 21, 77, 118
 diseases 235
 Sleep disorders 273
 Smooth muscle 91, 109, 118, 333
 relaxation 191
 Sodium
 borate 470
 channel blockers 196
 etidronate 222
 fluoride
 gel 455
 paste 455
 fusidate 391, 392
 nitroprusside 176
 perborate 462, 473
 stibogluconate 429
 valproate 304
 Solubility of drug in tissue 286
 Somatic
 gene therapy 61
 nervous system 67
 pain 321
 Somatostatin 209
 Sore throat 409
 Sotalol 85, 87, 198
 Spansules 13
 Sparfloxacin 388
 Spastic neurological disorders 106
 Spectinomycin 382
 Spectrum of activity 368
 Spinal anesthesia 112
 Spirochetes 437
 Splenic capsule 76
 Stages of general anesthesia 284
 Stannous fluoride 455
 Staphylococcal infections 368, 384
 Status
 asthmaticus 135
 epilepticus 303, 306
 Status of oral antidiabetics 230
 Stavudine 405
 Steady state plasma concentration 33
 Sterilization 469
 Steroidal
 estrogens 238
 hormones 208
 Stimulant purgatives 265
 Stokes-Adam's syndrome 80
 Stool softening agents 265
 Streptococcal infections 368, 384
 Streptogramins 391, 392
 Streptokinase 153
 Streptomycin 381, 395
 Strontium chloride 455
 Strychnine 332
 Stuffy nose 409
 Subacute bacterial endocarditis 381
 Succinimides 304
 Succinylcholine 105
 Sucralfate 258
 Sufentanil 328
 Sulbactam 373
 Sulfamethoxazole 365
 Sulfinpyrazone 354
 Sulfonamide 363, 419, 423
 Sulfonanilide derivatives 346
 Sulfones 423
 Sulfonyleureas 229
 Sulindac 342
 Sulphasalazine 350
 Sulphone 419
 Sulpiride 320
 Sumatriptan 124, 125
 Suramin sodium 430
 Swine flu 409
 Sympathetic nervous system 74
 Sympathomimetic amines 202
 Synapse 68
 Synthesis of estrogen 238
 Synthetic and semi-synthetic 5
 Synthetic
 androgens 244
 competitive blockers 104
 prostacyclin 156
 Syphilis 368, 369, 384
- ## T
- Tachykinins 322
 Tachyphylaxis 48, 52, 80
 Tacrine 94
 Tamiflu 409
 Tamoxifen 223, 240
 Tannic acid 456
 Tapeworms 428
 Taste disturbances 463
 Tazobactam 373
 Teicoplanin 391, 392
 Temazepam 296
 Temporal lobe epilepsy 300
 Tennins 5
 Terazosin 83, 85
 Terbinafine 414
 Terbutaline 133
 Terfenadine 28
 Termination of
 action 78
 pregnancy 242
 Testosterone 244, 246
 secretion 212
 Tetanus 106, 369
 vaccine 478
 Tetracaine 110
 Tetracyclines 374, 376, 417, 420, 458
 Theophylline 133
- Therapeutic
 failure 230
 index 45
 indications of penicillin 368
 uses of
 adrenaline 78
 cephalosporins 372
 estrogens and progestins 241
 gonadotropins 212
 window phenomenon 45
 Thiabendazole 426
 Thiacetazone 395
 Thiamine 487
 Thiazide related agents 162
 Thiazides 163, 167
 diuretics 162
 Thiocyanate 218
 Thionamides 218
 Thiopentone sodium 290
 Thiourelines 218
 Thioxanthene 319
 Thrombin powder 156
 Thrombolytics agents 153
 Thromboplastin powder 156
 Thrombosis 189
 Thromboxanes 120
 Thymol 472
 Thyroid
 function test 218
 hormones 214
 storm 218
 stimulating hormone 211
 Thyrotoxicosis 87
 Thyrotropin releasing hormone 209
 Tiagabine 305
 Tigemonam 372
 Timolol 85, 87
 Tincture iodine 472
 Tinidazole 416
 Tobramycin 381
 Tocolytic agents 251
 Tocopherols 486
 Tolazoline 83, 84
 Tolmetin 347
 Tolnaftate 414
 Topiramate 305
 Total loss of taste 463
 Toxoplasmosis 364
 Trachoma 364
 Tranquilizer 317
 Traveling sickness 262
 Traveller's diarrhea 268, 376
 Treatment of
 acute myocardial infarction 193
 asthma 135
 cerebral malaria 423
 cough 129
 diabetes mellitus 230
 diabetic ketoacidosis 230
 different forms of amebiasis 418
 digitalis toxicity 186
 dyspepsia 255
 epilepsies 305
 H. pylori infection 259

hypertension 178
 infestations 426, 428
 leprosy 400
 rheumatoid arthritis 348
 tuberculosis 396
 urinary tract infection 389
 xerostomia 463
 Tresiolan 455
 Tresivac 480
 Triamterene 164
 Triazolam 296
 Triazoles 413
 Trichomonas vaginitis 416
 Trichomoniasis 418
 Triflupromazine 262
 Trifluridine 403
 Trigeminal neuralgia 303
 Trihexyphenidyl 99
 Trimethaphan 174
 Trimethoprim 363-365, 423
 Trinitazidine 192
 Trimovax 480
 Triphenylmethane dyes 473
 Troglitazone 229
 Trypanosomiasis 430
 Tuberculoïd leprosy 399
 Tuberculosis 381, 387, 393
 Tuberculous-meningitis 394
 Tubular secretion 29
 Tubulus renalis 161
 Tularaemia 381
 Type of
 mouthwashes 456
 shocks 200
 Typhoid 366, 369, 372
 fever 378
 Typhus vaccine 479

U

Ulcer protectives 258
 Ulcerative colitis 364
 Ultraviolet
 light 470
 rays 455
 Unstable angina 189
 Ureteric colic 260
 Uric acid 351
 synthesis inhibitor 353
 Uricosuric drugs 354

Urinary
 analgesic 390
 bladder 325
 distention 92
 tract infection 364, 365, 369, 387
 Urokinase 155
 Uses of
 anticholinesterases 94
 anticoagulants 153
 atropine 98
 centrally acting muscle relaxants 106
 cholinomimetics 93
 local anesthetics 111
 plasma expanders 204
 tocolytics 251
 wrong vehicle for infusion 54
 Uterine
 relaxants 75, 251
 stimulants 249
 Uterus 77, 241

V

Vaccines 477
 Vagina 241
 Vagus 325
 Valacyclovir 404
 Valporate 305
 Valproic acid 304
 Vancomycin 391, 458
 Variant angina 189
 Varicella vaccine 481
 Vascular smooth muscle 77, 175
 Vascularity of absorbing surface 20
 Vasoconstrictor agents 457
 Vastus lateralis 14
 Venlafaxine 314
 Verapamil 198
 Viagra 246
 Vidarabine 404, 408
 Vigabatrin 305
 Vinblastine 447
 Vinca alkaloids 447
 Vincristin 447
 Viomycin 396
 Viper russel snake venoms 157
 Viral vaccines 480
 Visceral pain 321
 Vitamin 484
 A 485

B complex 487
 B₁ 487
 B₁₂ 141, 142, 489
 B₂ 488
 B₃ 488
 B₅ 488
 B₆ 488
 C 489
 D 220, 223, 485
 E 486
 K 156, 487
 Volume of distribution 24
 Vomiting 305

W

Warning signs 409
 Water crystal theory 287
 Water soluble
 drugs 18
 vitamins 485, 487
 Weak
 acid 18
 androgen 244
 base 18
 Wernick's encephalopathy 273, 488
 Whitefields ointment 414
 Whooping cough 384
 Wood alcohol 275

X

Xerostomia 462

Y

Yellow fever vaccine 481
 Yinghaosu 423
 Yohimbine 83, 85, 246

Z

Zalcitabine 405
 Zaleplon 298
 Zero order kinetics 32
 Zidovudine 404
 Zileuton 347
 Zinc
 chloride 455, 456
 salts 474
 Ziprasidone 320
 Zolpidem 298
 Zopiclone 298

References for Further Study

1. Goodman & Gilman's: *The Pharmacological Basis of Therapeutics*, McGraw-Hill, New York.
2. Bertram Katzung: *Basic and Clinical Pharmacology*, McGraw-Hill, Boston.
3. Bennett PN & Brown MJ: *Clinical Pharmacology*, Churchill Livingstone.
4. Rang HP, Dale MM, Ritter JM, Moore PK: *Pharmacology*, Churchill Livingstone, Edinburgh.
5. Walton John G, Thompson John W: *Textbook of Dental Pharmacology and Therapeutics*. Oxford Publication.
6. KD Tripathi: *Essentials of Medical Pharmacology*, Jaypee, India.
7. Chaudhari SK: *Quintessence of Medical Pharmacology*, Central, India.
8. Sharma & Sharma: *Textbook of Pharmacology*, Paras, India.
9. Arvind Singh Panwar & Deepak Saxena: *Preparatory Manual of Medicine*, National Book Depot, India.
10. Satoskar RS, Bhandarkar SD & Ainapure SS: *Pharmacology and Pharmacotherapeutics*, Popular Prakashan, India.
11. Barar FSK: *Essentials of Pharmacotherapeutics*; S. Chand, India.
12. *Current Medical Diagnosis & Treatment*: Lange Publication.
13. Remington's *the Science and Practice of Pharmacy*, Lippincott Williams and Wilkins.
14. National Medical Series for Independent Study (NMS) Pharmacology, India.
15. Harrison's *Principles of Internal Medicine*: McGraw-Hill, New York.
16. Mosby's Drug Reference: Gage & Pickett Publication.
17. Martindale: *The Complete Drug Reference*, Pharmaceutical Press.
18. *Drug: Facts and Comparisons*, Wolters Kluwer Health, Inc, St Louis.
19. Essential Medicines, WHO Model List, Geneva.
20. British National Formulary, BMJ Publication, London.
21. Herfindale & Gourley: *Textbook of Therapeutics*, Lippincott Williams and Wilkins.
22. Sharma S, Sethi GR, Sachdev GK, Gupta U, Gulati RK: *Standard Treatment Guidelines*, New Delhi.
23. Padmaja Udaykumar, *Short Textbook of Pharmacology for Dental Students*, Jaypee, Delhi.
24. Naresh Kumar Khanna, *Principles of Dental Pharmacology*, CBS Publication, Delhi.
25. Indian Journal of Pharmacology, Medknow Publication, Mumbai.